Lithiumaluminiumhydride reductions and their analogy to Grignard reactions

DISSERTATION

SUBMITTED FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

TO THE PHILOSOPHICAL FACULTY, SECTION II

OF THE

UNIVERSITY OF ZURICH

BY

K. N. SAREEN

OF SRINAGAR (KASHMIR), INDIA

APPROVED BY PROFESSOR DR. PAUL KARRER

ZÜRICH 1952

BRUNNER & BODMER

Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41507222_0102

Lithiumaluminiumhydride reductions and their analogy to Grignard reactions

DISSERTATION

SUBMITTED FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

TO THE PHILOSOPHICAL FACULTY, SECTION II

OF THE

UNIVERSITY OF ZURICH

BY

K. N. SAREEN

OF SRINAGAR (KASHMIR), INDIA

APPROVED BY PROFESSOR DR. PAUL KARRER

ZÜRICH 1952

BRUNNER & BODMER

R. UNIV.
BIBLIOTHEEK
LEIDEN

To
Kuldip and Lila
to whose unlimited sacrifices
this work owes its existance

ACKNOWLEDGEMENT

The practical work of this dissertation was carried out in the Institute of Chemistry of the University of Zürich, under the direction of

Professor Dr. Paul Karrer

to whom I am deeply grateful for his guidance, interest, and an unbound help and benevolence he has accorded.

I feel grateful also to Dr. R. Schwyzer for his valuable advice and to all my laboratory colleagues, especially Drs. D.K. Patel and Naval J. Antia, for the suggestions they made during the course of this work. I am deeply indebted to Drs. P.C. Dutta and Robert Schwyzer and to all my friends whose generosity and help at the time of my need made this work possible.

I express my thanks to Dr. Miss G. Bussmann and Mr. H. Frohofer of the microanalytical laboratories of the institute for the microanalyses reported in this work and their fine spirit of cooperation and friendliness.

CONTENTS

Introduction:

(a) $LiAlH_4$ reductions; 5

(b) Analogy to Grignard reactions; 14

(c) Reaction mechanism. 17

Present investigation: 21

(a) Desoxysugars:

1. Mannitol series; 22

2. m-Inositol series. 26

(b) Desoxysteroids:

1. 4-Hydroxycholesterol; 30

2. Δ^5-Pregnene. 39

References 41

Introduction

"Old order changes yielding place to the new" seems to be particularly true in Organic Syntheses where every new elegant reagent that affords better selectivity and milder reaction conditions brings the organic chemist nearer his goal of copying Nature in the remarkable syntheses it performs in its wonderful laboratories- the animal and the vegetable kingdoms. $LiAlH_4$ is one of the milestones on the road to this achievement.

Though simple hydrides as those of sodium and calcium were known since long, they had not been used to reduce organic substances mostly due to their insolubility in organic solvents. It was only after the discovery by H.I. Schlesinger, in 1947, of $LiAlH_4$[1] which was found to be soluble in ether that their strong reducing power could be used for this purpose. Subsequent studies[2] proved it to be so useful as to make it a "universal" reducing agent for organic compounds. This success prompted enquiry about the reducing properties of other allied hydrides and resulted in $LiBH_4$ and $NaBH_4$[3] which are more useful in the field of selective reduction.

$LiAlH_4$, prepared from LiH and $AlCl_3$ in ether or from Li_2O in industry[4], is a colourless to grey microcrystalline "ionic hydride" whose structure is not yet definitely established. It is soluble in ether (13-25%), tetrahydrofurane (13 %), dibutyl ether (2 %) and dioxane (0.1 %), insoluble in other organic solvents as benzene, chloroform, pet.ether, and decomposed by active-H compounds. A comparision with the other allied hydrides also used for reducing organic substances shows that the stability and the ether solubility is directly proportional to the polar character, and that in this respect $LiAlH_4$ occupies a middle position between the "molecular hydride" B_2H_6 and the polar $NaBH_4$.

Property	$LiAlH_4$	$LiBH_4$	$NaBH_4$
Decomposition Temp.	125-50°	250-75°	above 400°
Solubility in ether	25-30 %	3-4 %	Insoluble
Action of alcohol	D e c o m p o s e s		Sol. in MeOH
Action of water	Violent decomposition		Sol. in ice-cold water,
Reducing power	All C=hetero-atom comps.	>CO easily, −COOet with difficulty	Only > CO and −COCl are reduced
Order of polarity	$B_2H_6 < Al(BH_4)_3 < Be(BH_4)_2 < LiAlH_4 < LiBH < NaBH_4$		

The mechanism of reduction of Raney Nickel, an "interstitial hydride" and other catalysts as Pt, Pd, Ni, differs from that of $LiAlH_4$ in that the activity of the former is due to atomic hydrogen and surface activity, while of the latter to hydride ion $H^{\ominus}$ or the complex ion $[AlH_4]^{\ominus}$, which acts as a potential source of the active entity, the $H^{\ominus}$, which being strongly nucleophilic, donates its electron to the electron-deficient centre of the substrate.

Technique of its use is the same as of the Grignard reagent, an ether-solution of the substance being dropwise added to a stirred solution of $LiAlH_4$ in ether. In the case of ether-insoluble or difficultly soluble substances as some halides, tosylates and amides tetrahydrofurane is employed though N-ethylmorpholine and diethyl- and dibutylcarbitols (Diethyleneglycol diethyl-, and dibutyl ether) have also been reported. N-methylmorpholine and isopropylether were found to be unsatisfactory. The use of Soxhlet Extractor or a use of benzene-ether mixture has also proved successful. For highly unsaturated substances as polyenes, or for the purpose of selective reductions, sub-zero temps. are used. Some 10-15 % excess of $LiAlH_4$ is generally employed and for active-H centres an equivalent amount is allways taken into account. After the reaction is over, the excess of the reagent and the intermediate complex are decomposed with cold water, ethyl acetate or ammonium-chloride. Further working up depends upon the nature of the reduction product. The precipitated $Al(OH)_3$ can be filtered, using Celite or Hyflo SuperCel, or can be dissolved in dil. H_2SO_4 or (NaOH for acid-sensitive substances as acetals etc.) and then extracted with ether. In the case of water-soluble reduction products, filtering, extracting the alumina with the appropriate solvent, and working up the dried residue left after evaporation has also been employed.

The importance of $LiAlH_4$ lies in its capacity of selectively reducing C=heteroatom bond as against the C=C bond and in that these reductions proceed quickly, under mild conditions, in excellent yield, even in sterically hindered cases and in one steric sense. The order of reactivity of the various functional groups is roughly as: Carbonyl > acid chlorides and anhydrides > esters and lactones > acids > N-containing compounds as amides, nitriles and oximes > halides. A brief review of these reductions which are almost exactly analogous to the Grignard reactions, is given below followed by the "reaction mechanism".

A. Active-hydrogen compounds:[5] Like Grignard reagent, it is decomposed by water, alcohols, amines and other active-H compounds and is hence used in Zerewitinoff-estimations also.

B. Carbon-Oxygen Bond:

(a). C=O bond:

1. Carbonyl group: As with the Grignard reagent, the aldehydes and the ketones are reduced to alcohols.[6]

$$4RCHO + LiAlH_4 \longrightarrow LiAl(OCH_2R)_4 \xrightarrow{H_2O} 4RCH_2OH$$

A variety of ketones including those of the condensed rings[7], steroids[8], terpenes[9], heterocyclic compounds[10] and even some highly hindered ketones[11] have thus been reduced. It gives mainly one stereoisomer[12], while $LiAlH_4$-d-camphor yields optically active alcohols[13]. The direct complete reduction of $>CO \rightarrow CH_2$ has been reported only in o-p-amino- or methoxy aromatic aldehydes and ketones[14], (for indirect reduction see under tosyl esters). α-β-unsaturation[15] and the cyclopropane ring[16] generally remain unaffected and bifunctions as 1:2-, 1:3-, 1:4-diketones, quinones[17], and the further removed keto groups as in Karrer's 1:6-diketone[18] (C_8-ketone of carotinoid syntheses) are all normally reduced to the diols. Cyclohexan-1:2-dione, however, gives only cyclohexanolone[19] and the unsaturated 1:4-diketones[20], as with the Grignard reagent, undergo predominantly 1:4-additions, whereas Meerwein-Ponndorf reagent gave 1:2-addition products. α-Haloketones[20a] give halohydrins by 1:2-addition in contrast to the reductive elimination of the halogen by 1:4-additions by the Grignard reagent. The selective reductions[21] of some bifunctions have been affected with a calculated quantity of $LiAlH_4$ under very mild conditions or better with $NaBH_4$. Protection of keto groups, especially in steroids, is afforded by acetals[22], thioacetals, enolethers[23], and thioenolethers[24] which are immune to the action of the reagent.

2. Carboxyl group: Even a free acid[25] is reduced under mild conditions and in a good yield to the primary alcohols (analogy to the Grignard reaction).

$$4\ RCOOH + 3\ LiAlH_4 \longrightarrow LiAl(OCH_2R)_4 \longrightarrow 4\ RCH_2OH$$

Before this these had been reduced only through the HI, the Bouveault-Blanc or the drastic copper chromite reductions of the esters which was specially unsatisfactory in the case of the unsaturated acids. In o-p-amino aromatic acids the carboxylic group is directly reduced to the methyl group[14] (for similar reductions of amino acids of aliphatic series, see under tosyl esters). The keto-[26], the hydroxy-[27], and the dicarboxylic acids[26] give the diols (2-desoxychinovic acid[28] gives only the hydroxyacid), and the aminoacids[29] give the aminoalcohols. α-β-unsaturation[30] is not affected and even sterically hindered acids[31] yield to the reduction.

3. The acid chlorides[32] and the anhydrides[33] are very easily reduced to the primary alcohols (analogy to the Grignard reaction).

$$2\ RCOCl + LiAlH_4 \longrightarrow LiAlCl_2(OCH_2R)_2 \longrightarrow 2\ RCH_2OH$$
$$(RCO)_2O + LiAlH_4 \longrightarrow LiAlO(OCH_2R)_2 \longrightarrow 2\ RCH_2OH$$

Even hindered ones[26] yield to the reduction. Partial reduction of the anhydrides with calculated amount of $LiAlH_4$ yields lactones[34], while that of the anhydrides and the chlorides with LiH gives the aldehydes[35].

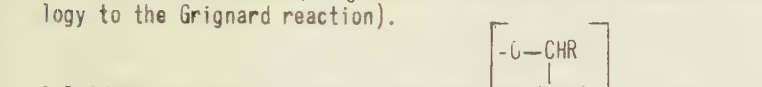
4. The esters smoothly give the primary alcohols[36] (analogy to the Grignard reaction), the reduction being easier than that of the free acids.

$$2\ RCOOR' + LiAlH_4 \longrightarrow LiAl(OCH_2R)_2(OR')_2 \longrightarrow 2\ RCH_2OH + 2\ R'OH$$

A variety of esters including those of polynuclear hydrocarbons[37], heterocyclic compounds[38], steroids[39] and terpenes[40] have thus been reduced. In the case of a keto-quinolizidine derivative, however, the replacement of the ester group by a hydrogen atom was noticed[41] (here $CuCr_2O_4/H_2$ also gives the same results), while in 2-amino-5-carbethoxythiazole and o-p-amino- and methoxy-aromatic esters[14] the ester group was directly replaced by a methyl group through the intermediate alcohols. Similar results have been obtained in the aliphatic aminoacids through the tosyl esters of the intermediate carbinols. The reduction of the optically active esters without recemisation has been applied by Karrer[42] to obtain optically active α-aminoalcohols, by Reichstein[43] in the steroids and by Stoll[44] in lysergic acids. The cyclopropane ring remains unaffacted and the similar unreactivity of the α-β-doublebonds has been much used in the vitamin-A[45], corticosteroids[46] and the other allied fields[47]. The enolesters[48] give the normal enols, benzyl esters[49] benzyl-alcohol. diesters

diols and the methylated uronic acids[50] the aldoses. Thiolesters[51], too, are reduced to the alcohols, but the method is inferior to the Raney-Nickel desulphurization. It is interesting, however, to compare this with their LiH-reductions to aldehydes[35], which reminds of the similar partial reductions of the acid chlorides and the anhydrides to aldehydes with the same reagent. This weakened reaction of LiH as compared with $LiAlH_4$ is parallel to the reduction of thiolesters to aldehydes with poisoned Raney-Nickel, while the normal catalyst takes it to the alcohol stage. In bifunctions, selectivity has been achieved either in the case of primary-tertiary diesters[52], or by the use of $LiBH_4$ or better $NaBH_4$[53].

5. The lactones: β-γ-and δ-lactones[54] are reduced to the diols (analogy to the Grignard reaction).



Even complex lactones as podophyllotoxin and picropodophyllin[55] give normal results. The reduction of α-β-unsaturated lactones of cardiac aglycones, of azlactones and the partial reduction of lactones has not been reported.

6. The Amides[56] are smoothly reduced to the corresponding amines containing the same number of carbon atoms (cf. Hofmann and Curtius degradations).

$$2\ RCONH_2 + LiAlH_4 \longrightarrow 2\ RCH_2NH_2 + LiAlO_2$$

This apparent difference from the Grignard reaction is no exception to the general analogy and has been explained later. Previously the amides had been reduced only under drastic conditions over $CuCr_2O_4$ in very bad yields whereas now even the hindered amides[57] and imides[58] can be easily reduced. The partial reduction of the lactams to aldehydes has been achieved using a calculated amount of the reagent[59]. Anilides give secondary amines and this N-acylation and subsequent reduction provides an alternative procedure of N-alkylation[60], as N-methylation via N-formylation. This and similar reductions of the lactams have been much used particularly in the alkaloid chemistry[61], where (-) oxysparteine has been reduced to (-)sparteine, strychnine to strychnidine, and N-substituted oxindoles, with spontaneous ring closure, to yohimbine ring system. (The reduction of N-substituted oxindoles gives only some 15 % of the normal dihydroindole, the rest being indole arising from the dehydration of the intermediate 2-hydroxy compounds produced by the normal reduction of the >CO group). N-unsubstituted oxindoles are inert to reduction. Similarly N-substituted isoquinolone[62]-and phenanthridone[63] rings gave the dihydro products; N-unsubstituted dihydrocarbostyril[64] gave benz (cd) indolines (the

latter correspond to the lysergic acid skeleton) and cyclanon-isoximes[66] the large ring polymethylene imines. Likewise hydantoins[67] were made to yield imidazolones and the tertiary amides the aldehydes[68]. The reduction of other miscellaneous acid derivatives as amidines, hydrazides, azides and diazoketones has not been reported.

(b). C-OH bond: Alcohols, as a rule, are not further reduced though in some cases of activated -CHOH- groups[69] $LiAlH_4$, like the catalytic hydrogenation, reduces these to the $-CH_2-$ stage. For indirect reduction see under tosyl esters.

(c). C-O-C bond: The ether linkage.

1. Acyclic: Normal aliphatic and aromatic ethers are stable and are used as solvents. Even an increase in the electronegativity on the adjoining carbon atom as in benzyl, benzhydryl and trityl ethers, which usually makes them susceptible to polar reagents and catalytic hydrogenation, is insufficient to cause a fission of the C-O bond[70]. Same is the case with the acid-sensitive bis-ethers (gem-diethers as methyleneoxy compounds, acetals[22] and glycosides) and tris-ethers as ortho esters. The effect of $CoCl_2$ on these is not known. Vinyl or enol ethers are generally stable as in thebaine[71] and in some C_3-steroids[23] though in some cases as corynantheine[72] and some acyclic[72] and cyclic[73] 1:3-diketones the fission does occur. Likewise the allylic ethers[74] are also stable though in thebaine[71,71a] the furane ring opens up. (G. Stork[75], on the basis of his spectroscopic work, doubts the structure proposed for dihydrothebaine obtained by this ring opening ?). Karrer's use of $CoCl_2$-catalyst in breakting benzyl- and allyl phenyl ethers clearly brings out their analogy with the similar Grignard reactions[76].

2. Cyclic. Like the Grignard reagent, $LiAlH_4$ reduces the epoxides[77] to the alcohols.

$$4\ RCH\text{-}CH_2 \quad (O) \quad + \quad LiAlH_4 \longrightarrow LiAl\left[\begin{matrix} CH_3\text{-}CHR \\ \quad\quad | \\ \quad -O- \end{matrix}\right]_4 \longrightarrow 4\ \begin{matrix} RCH\text{-}CH_3 \\ \quad\quad | \\ \quad\ OH \end{matrix}$$

The method is thus an alternative to the earlier hydrogenolysis, Raney-Nickel dehalogenation or desulphurization of the hydrogen halide or the thiol-adducts. The mode of their fission[78] depends upon the reagent used, the unsymmetrical primary secondary and secondary tertiary epoxides exclusively giving secondary and tertiary, while catalytic hydrogenation or Raney-Nickel/alkali furnishing the primary and the secondary alcohols. The symmetrical disecondary epoxides follow the same fission as with catalytic hydrogenation. The occasio-

nal complete elimination of the oxido - oxygen as met with in energetic catalytic hydrogenation has not been observed with $LiAlH_4$, but subsequent high temp-vacuum sublimation may achieve this end as in cinchonamine[79]. The carbon-analogue, cyclopropane ring, is stable, while the corresponding nitrogen-and sulphur-analogues, aziridine (ethylenimine, and ethylene sulphide, have not been tried. The fission of epoxides, which takes place with inversion of configuration[19] (S_{N2} type) has been much used in the carbohydrates for obtaining desoxysugars[80] and in the steroids[78] for introducing -OH group at C_5, C_6, C_{11}, C_{17}, C_{21}-positions. H. Schmid's epoxide[81] (of 3-methyl-A-norcholestene; 3,5) was an exception. King's alternative route[82] to steroid epoxide reduction through their isothiouronium tosylates seems to be interesting.

(d). C-O-O-C linkage: A solitary example of the fission of the ozonides to diols has been provided by Stoll[83], but that of the peroxides is not known. For azo-, amino- and sulphoxides, see later.

C. Carbon-nitrogen bond:

1. The amines: Primary and secondary amines behave as active-H compounds, and tertiary amines can form the addition compounds (analogy to the Grignard's).

2. Quarternary ammonium salts: The conversion of strychnine methosulphate to strychnidine[84] shows that in the saturated cyclic ones an exocyclic C-N bond fission occurs displacing the methyl group, which is more susceptible to nucleophilic attack than the higher alkyls[85], as methane. (Here the lactam group was simultaneously reduced). The same is the case with the saturated acyclic ones as ammonium chloride, though other examples have not been reported. Curiously, it is analogous to the catalytic hydrogenation of 7-hydroxy-8-piperidinomethyl-tetrahydroisoquinoline to the 7-hydroxy-8-methyl compound[86], used as the starting material in Woodward's synthesis of quinine and thus seems to be of use as a general method for the degradation of $R_4N\,X$ to R_3N. It remains, however, to be seen whether the presence of a higher exocyclic alkyl group would favour an endocyclic C-N bond fission thus affording a mild alternative to Emde's and von Braun's degradations. The unsaturated cyclic bases, on the other hand, are smoothly reduced to their o-dihydro products and the reaction has been much used in other heterocyclics and alkaloids[87]. Even such sensitive compounds as vitamin-B_1 and cozymase yielded the dihydro derivatives (the latter with $NaBH_4$ in place of the earlier sod.dithionate). All these results find an exact analogy with the Grignard reactions. It is of interest, however, to compare these reductions with those by formic acid[88] and Raney-Nickel/Et_2NH[89] to the corresponding tetrahydro products.

(b) C=N bond: The oximes[90] and the aldimines[17b] are reduced to the corresponding primary and secondary amines, and phenanthridine[91], though a cyclic tertiary amine, gives 5:6-dihydro compound isocyanides may give the same results (not yet reported).

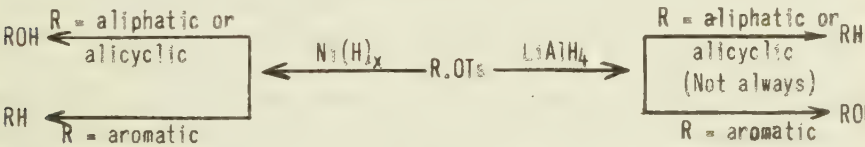
(c) C≡N bond: Nitriles[92] are reduced to the primary amines in good yield, without secondary or tertiary amines as by-products. The use of 1:1 mol[92a] $LiAlH_4$ (earlier 1:1/2 mol ratio has been contradicted) shows the reduction to be exactly analogous to the Grignard additions. Conjugated double bonds remain unaffected, hindered nitriles are easily reduced and a partial[93] reduction leads to aldehydes (cf. Stephen's reaction). Dinitriles and cyanohydrins give the diamines and the α-aminoalcohols though in bad yield due to the precipitation of the intermediate complex. This difficulty may be overcome by using high boiling solvents. Acetylation of the cyanohydrins gives better yields[94].

D. The Nitro compound[17b,36]: Aliphatic nitro compounds smoothly give the primary amines, the conjugated double bonds[95], if present, being invariably reduced (used for preparing β-phenylethylamines). The selective reduction of a nitro group in presence of a double bond has also been achieved[96]. The aromatic ones readily give the azo compounds and the azo-and the aminoxides yield the azo compounds and the amines. The azo-and the hydrazo compounds are unaffected.

E. The Halogen compound[97]: As with the Grignard reagent, these are hydrogenolysed to the corresponding hydrocarbons. Even LiH, in the presence of a small amount of $LiAlH_4$, can work showing that the latter here acts only as a carrier of the chain reaction. The reactions take place better in tetrahydrofurane than in ether and require a little higher temp and a longer time but are still milder than the earlier reductions. Thus cis-and trans-1:3-dichloropropenes give the corresponding 1-chloropropenes without rearrangement and theuse of $LiAlD_4$-LiD converted (-)phenylmethyl-carbinyl chloride into (-)α-deutroethylbenzene- the first simple optically active compound of the type R_1R_2CHD[98]. The order of reactivity is I>Br>Cl and Primary>secondary>tertiary. Vinyl, alicyclic and aromatic halides are resistant, while the allylic are activated. The oxonium chlorides smoothly gibe the o-dihydro products[99] (cf. the quart. ammonium salts).

F. The Sulphur compound[100]: The C-S bond has in most cases been found to be very resistant to the action of $LiAlH_4$, while the S-S and the S-O bonds do give way yielding mostly the -SH compounds. Thus (a) mercaptans and thiophenols are unaffected. They only decompose $LiAlH_4$ by their active-hydrogens. The sulphides, thioacetals and thioenolethers, too, remain unaffected. Thiolesters[51] are, however, reduced to the alcohols, and the thiocyanates give the mercaptans

(both these being the effect of unsaturated carbon on one side). The di- and trisulphides are also reduced to the mercaptans, better in tetrahydrofurane, and the method has been used for their quantitative estimations. (b) Sulphoxides are not reduced in ether, while so far only the 5-membered ring sulphones under mild conditions and their open chain and 6-membered analogues[100] at higher temperature have been reduced to the corresponding sulphides. α-disulphones likewise give the disulphides. (c) Sulphenic acid chlorides, sulphinic acids and their chlorides and thiosulphonic esters give disulphides which originate [illegible] through some secondary reactions. (d) Sulphonic acids and their amides remain unaffected while their chlorides are easily reduced to the mercaptans. On the other hand, the sulphonic esters[101], like the halides, to which they resemble in many other respects too, as their reaction with the Grignard reagent, sod.iodide, silver nitrite, dehydrotosylation, and their use in the Darzen condensation, undergo hydrogenolysis to the corresponding hydrocarbons. Their fission has, however, been shown by H. Schmid and P. Karrer to be of two different types: many alkyl tosylates were hydrogenolysed while the aryl tosylates underwent hydrolytic fission. Thus l-menthane, diacetone D-galactose-, cholesterol-, and codeine-tosylates gave l-menthane, diacetone D-fucose, Δ^5-cholestene (+i-cholestene from the mesomeric cholesteryl-cation) and desoxycodeine-E, while phenol tosylate gave phenol. The hydrolytic fission of some sugar derivatives was considered to be due to steric hindrance effect which was also seen in their reactions with sod.iodide and the Grignard reagent. Mesyl esters[100] behave similarly. These results, along with their reverse hydrogenolysis with Raney-Nickel[102], have thrown much light on the mechanism of $LiAlH_4$-reductions in general.



G. C=C and C≡C bonds: An isolated or unpolarised C=C bond remains unaffected except[103] in systems, Ar.Ch=CHX and RCH=CX_2 (X= a strong polar reducible group) as in cinnamic aldehyde and its acid, o-hydroxycoumaric ester, β-nitrostyrene, ω nitro-2-vinylthiophene, and isoamylidene-α-cyanoacetic ester though those in cinnamic alcohol and its ester remain unaffected at -10°, in allyl alcohol get reduced at higher temp in a very bad yield and in polyene carbonyl compounds, their acids and esters are quite stable. In such cases, too, lower temp, reverse method of addition, a calculated amount of $LiAlH_4$, and a shorter reaction-time can save the double bond. A conjugated triple bond as in cyclohexenylbutinol[104] is partially reduced to a double bond giving a diene system. Aromatic hydrocarbons as naphthalene, anthracene and phenanthrene remain unaf-

fected in ether and tetrahydrofurane, though solid $LiAlH_4$ when added to molten anthracene at 225° gives some 9:10-dihydro product [105]. Earlier report of both phenanthrene and anthracene giving the dihydro-and the tetrahydro compounds has now been contradicted[106] The reaction with anthracene takes place only at a temp above the decompsition point of $LiAlH_4$ and even then is associated only with its mesco activity leading to a stable product w th two benzenoid rings proving that a true benzenoid nucleus has never been reduced by this reagent. Likewise the heterocyclic rings, too, remain unaffected.

H. Miscellaneous: $LiAlH_4$ has also been used for preparing other rare hydrides, organometallic compounds and hydrogen deuteride[108], and for reducing CO_2 to methanol[109] (useful especially in radio-tracer field), and nitric oxide to hyponitrous acid[110].

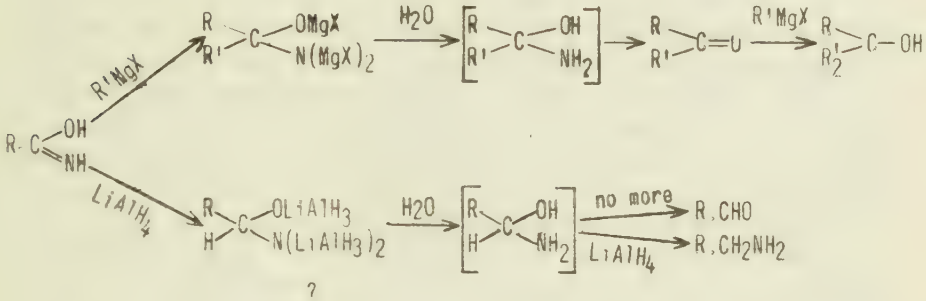
ANALOGY to GRIGNARD REACTIONS[111]

In its reactions $LiAlH_4$ is exactly analogous to the Grignard reagent as is shown by its decomposition by active-H compounds and thence its use in the Zerewitinoff estimations, by its forming addition compounds with the ethers and tertiary amines, its giving a positive Gilman-Schultz carbon-metal linkage test[17b], and its reactions with metallic compounds to give the other hydrides. Being anionoid like the later, it shows the same unreactivity towards other anionoid centres as the isolated C=C and C≡C bonds, cyclopropane ring and the aromatic and the heterocyclic nuclei; though in contrast to the Grignard reagent it converts the conjugated enynes to the diene systems. Further, both react with the alkyl halides in the same way and the analogy goes to such an extent that only those halides react with it which also react with the Grignard reagent. The order of reactivity of the various halides and the indifference to the vinyl halides is the same, though the alicyclic and the aromatic halides do react with the Grignard reagent. Alkyl tosylates, which resemble the halides, are hydrogenolysed in the same way and even in aryl tosylates the same S—O bond is broken.

$$C_6H_5OMgX + R\text{-}SO_2C_6H_4CH_3 \xrightarrow{\bar{R}\,\overset{+}{M}gX} C_6H_5O\text{-}SO_2\text{-}C_6H_4.CH_3 \xrightarrow{Li^+[AlH_4]^-} C_6H_5OH + H.SO_2C_6H_4CH_3$$

Their addition to the C=O is the same in aldehydes, ketones, acids, their chlorides, anhydrides, esters, lactones and the amides. α-β-unsaturated ketones give predominantly 1:4-addition products with both of them. The intermediate carbonyl compound from the lactones as isolated in the case of the Grignard reagent has, however, not been reported with $LiAlH_4$. The conversion of

amides to amines which apparently seems to be a case where $LiAlH_4$ and the Grignard reagent differ in their reactions is not an exception to the general analogy for both proceed through the same mechanisms.



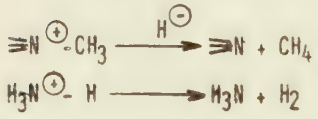
That amides react in their tautomeric forms and give aldehyde-ammonias as an intermediate —— though in no case their isolation has been reported, perhaps due, like their parent carbonyl compounds, to their extreme reactivity towards $LiAlH_4$ ——is supported by the following evidence:
(i) In the case of tertiary amides[68] and lactams[59] the use of a calculated amount of $LiAlH_4$ makes it possible to isolate these intermediate aldehydes (cf. the reduction of acid chlorides and the anhydrides with the weaker reagent LiH, where, too, the reaction stops at this intermediate stage)[35].
(ii) these aldehyde-ammonias are known to further get reduced to the amines (cf. "reductive alkylation of ammonia" with Raney-Nickel or Pt/H_2.

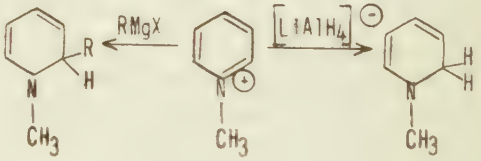
Rather their $LiAlH_4$-reductions would afford an elegant and milder alternative for the conversion $RCHO \longrightarrow RCH_2NH_2$).
(iii) $LiAlH_4$-reduction of an activated -CHOH- to $-CH_2-$, as required in aldehyde-ammonias, is a general phenomenon as also seen in o-p-aminobenzyl alcohols, 2-amino-carbethoxythiazole and α-aminoketones[14]. It is further supported by the reduction of acid anhydrides to the lactones[34] via the intermediate monocarbinols with a calculated amount of the same reagent.

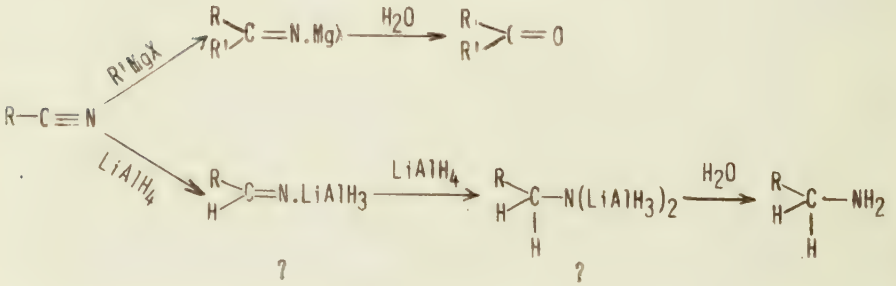
The normal aliphatic and the aromatic ethers, and the benzyl, benzhydryl, and the trityl ethers are indifferent to both the reagents, Späth's breaking up of some ethers with the Grignard reagent at 200° being an abnormal reaction. (cf. $LiAlH_4$-reduction of anthracene at 225°). Further, the epoxide fission with inversion of configuration is the same in both cases. The acetals and the orthoesters are stable to $LiAlH_4$ though the Grignard reagent decomposes these to ether-alcohols and even to the hydrocarbons[111a]. Whether the more polar $NaBH_4$ will affect these remains to be seen. In γ-pyrones the ether linkage breaks

(via the hemiacetals) with the Grignard reagent but the action of $LiAlH_4$ is not known. In the case of unsaturated ethers only in a few cases a comparative data is available. Some enolic ethers, as in C_3-steroids and thebaine, are stable to both the reagents (CH_3MgX breaks it, while C_6H_5MgX does not), while in some cyclic enolic ethers[73] fission occurs with both the reagents. In corynantheine and $CH_3\text{-}C(OCH_3)\text{=}CH.COOC_2H_5$, $LiAlH_4$ breaks the enolic ethers and the action of Grignard reagent is not known, while that in iminoesters is broken by the Grignard reagent and the action of $LiAlH_4$ is not known. The same is the case with the allylic ethers which are generally stable to both the reagents though in some cases, as in thebaine, both open up the oxide-bridge. Finally, the $CoCl_2$-catalytic fission of some ethers with both the reagents leaves no doubt as to their general analogous behavior.

Primary, secondary and tertiary amines react in the same way with both of them though the formation of α-substituted derivatives by the cyclic tertiary amines with the Grignard reagent at high temp has not been reported with $LiAlH_4$. The saturated quarternary salts react with both displacing the more anionoid-susceptible lower alkyl groups as hydrocarbons while the unsaturated cyclic ones undergo the same addition to the C=N bond giving the similar α-disubstituted derivatives. The addition to the C=N of aldimines and the oximes and that to the C≡N bond of the nitriles is exactly analogous in both the cases and the apparent difference in obtaining the amines and the ketones from the later is no exception.







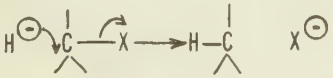
Their similar behavior towards the sulphur compounds is shown below:

	$LiAlH_4$	R'MgX
1. Mercaptans	Decomposition	
2. Disulphides	Mercaptans	Sulphides
3. Thiolesters	Alcohols	Alcohols
4. Thiocyanates	Mercaptans	Mercaptans + sulphides
5. Sulphoxides	Stable	Stable
6. Sulphones	Only a few react	Stable
7. RSCl, RSOCl, RSO_2OH, $RSO_2.SR$	Disulphides; then Mercaptans	RS.OR ⟶ RSR RSO.OR ⟶ RSO.R
8. Sulphonic Chlorides	Mercaptans	Different products.
9. " amides	Stable	Stable
10. " esters	Exactly analogous,	see above under Halides

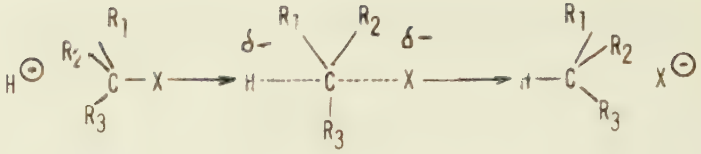
Finally the $LiAlH_4$-reduction of nitric oxide to hyponitrous acid finds an exact analogy in its conversion to nitrosophenylhydroxylamine by the Grignard reagent.

REACTION MECHANISM

A C—C bond is a nucleophilic centre and adds only the electrophilic reagents, while a C=O bond is electrophilic in nature and adds nucleophilic reagents. The known behavior of $LiAlH_4$ towards an isolated C=C bond and the C=O bond clearly shows it to be a nucleophilic reagent. Its analogy to the Grignard reactions and further its opening the epoxide ring with inversion of configuration proves that these reactions are "ionic" and of S_{N2} mechanism, i.e. bimolecular nucleophilic displacements of strongly electronegative elements as oxygen, nitrogen, halogens on carbon by hydrogen. It is very likely that the anion $[AlH_4]^{\ominus}$, furnished by the dissociation of the complex hydride, attacks the substrate where it acts as a potential source of the active entity, the hydride ion $H^{\ominus}$, which being strongly nucleophilic, donates its electron to the electron-deficient centre. These displacements take place according to the adiabatic Heitler-London mechanism[112] and in the case of compounds containing only the σ-bonds are depicted as:

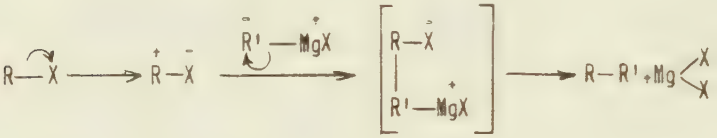


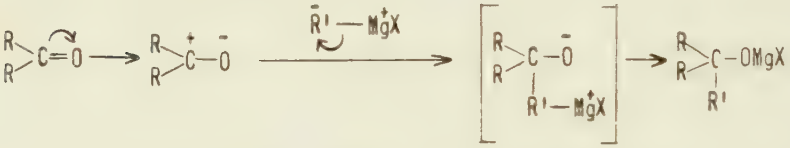
(i)



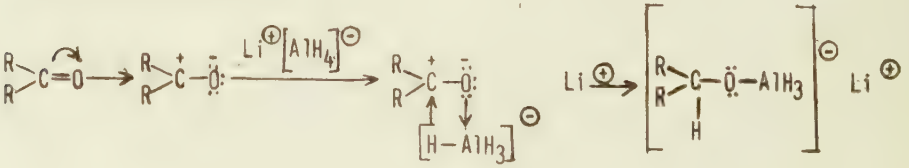
(ii) For cases of inversion of configuration while in those containing $\sigma+\pi$ bonds which form only a part of a multiple bond, the "displaced group" remains attached to the molecule by a bond of lower order.

Compare the analogous Grignard reactions:



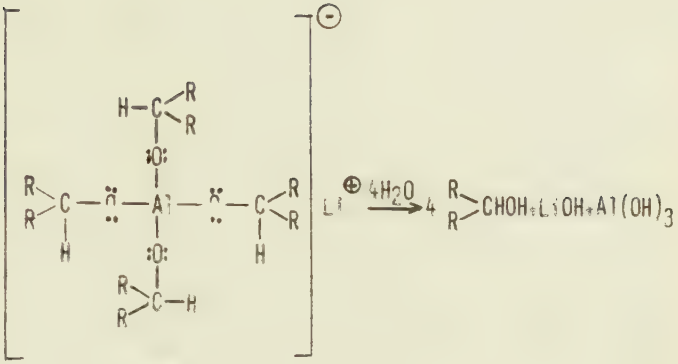


As in the case of the σ-bond, the $\sigma+\pi$-bond anionoid reactions, too, take place most readily if the "displaced atom" has higher electron affinity than carbon, and therefore the reactivity is most marked in compounds containing C=O, C=N, and C≡N bonds. Further the higher polarity of the carbon-oxygen bond than of carbon-nitrogen bond accounts for the order of reactivity of $LiAlH_4$ with these functional groups. The lack of evidence of the dissociation of $LiAlH_4$ and that of the knowledge of the structure of the intermediate complex has, however, led to the belief that the reactant is probably a series of complex aluminohydride ions AlX_nH_{n-4} (X = a reducible substance; and n progresses from zero to four during the course of the reaction), which acts as a carrier for the hydride ions[19].



Entry of three

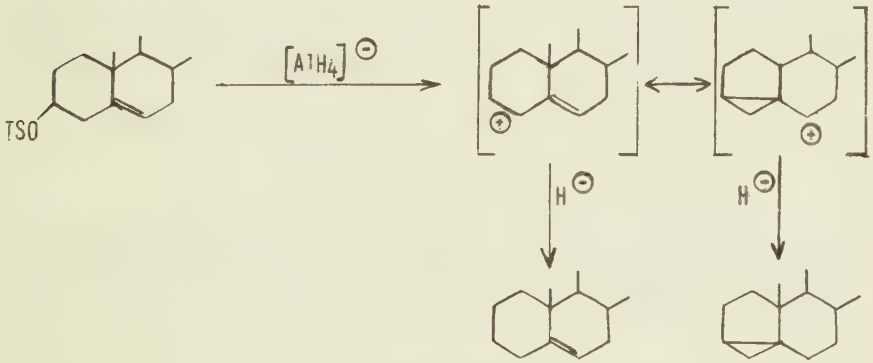
more keto groups in the same way



?

$LiBH_4$ and $NaBH_4$ are less active due to the greater stability of the borohydride ion, $[BH_4]^{\ominus}$, and thence of its reluctance to transmit the hydride fragment to the electrophilic centre of the substrate. This also explains their preferential reduction of C=O as compared with C=N or C≡N linkages.

(i) The heterolytic fission of alkyl halides and tosylates[71]:



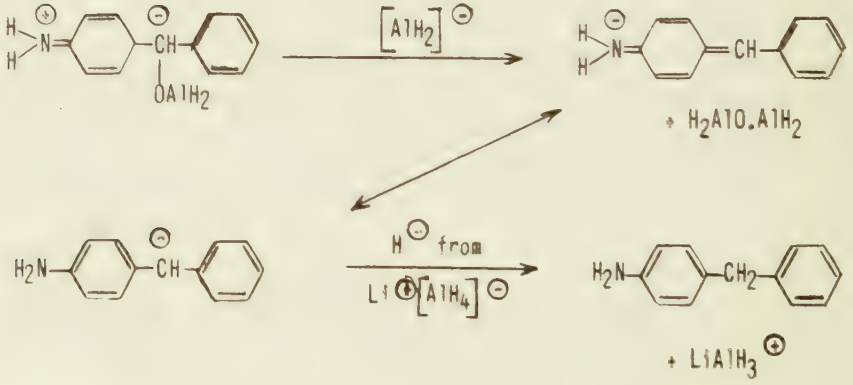
(the anion attacks both the mesomeric cholesteryl-cations);

(ii) The reduction of strychnine methosulphate to strychnidine where the methyl, which is more susceptible to nucleophilic attack than the higher alkyl groups, is displaced as methane[84];

(iii) A comparasion of $LiAlH_4$ with sodium ethylmalonate[19] with respect to the site of the reaction in unsymmetrical epoxides, where both preferentially attack at the terminal carbon;

(iv) The $LiAlH_4$ reduction of the 11-keto-, and 17-keto-steroids to β-ol configuration, where potassium acetylide and the Grignard reagent are known to open the π-bond by a S_{N2} rear-bond attack to give α-side-chain and β-OH compounds.

In the case of $\sigma + \pi$ bond compounds with -E [112] substituents as 2-amino-5-carbethoxythiazole and o-p-amino-arylcarbonyl compounds, acids and esters, where the oxygen function undergoes hydrogenolysis to the methylene and the methyl stage, the reaction probably does not proceed through a simple unimolecular ionization of $LiAlH_4$ as shown above. In such cases[14] the postulated mechanism involves attack on the oxygen of the intermediate carbinol by a positive ion such as $[AlH_2]^{\oplus}$, furnished by the reducing agent followed by scission of the C—O bond. This cleavage would be facilitated both by the -E substituent on the ring and the attacking positive ion. The resonance-stabilized carbonium ion thus formed the rapidly picks up a hydride ion $H^{\ominus}$ from the reducing agent giving the final product. The case of p-aminobenzophenone is illustrated below starting with the intermediate carbinol derivative.

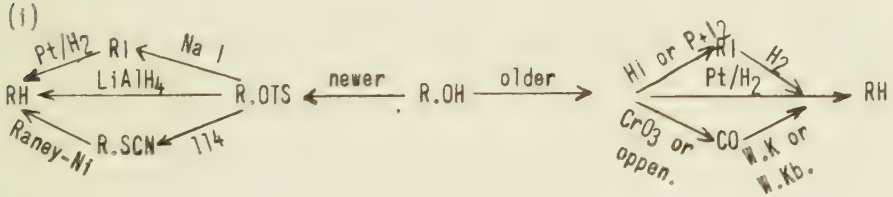


PRESENT INVESTIGATION

The behavior of a tosyloxy group as a chloride atom as shown by NaI/acetone[113] and other similar replacement reactions was coupled by H. Schmid and P. Karrer with the $LiAlH_4$ reduction of alkyl halides to affect a similar hydrogenolysis of the tosyl esters. The results of their experiments have already been described under "sulphur compounds". The present investigation started with the aim of studying this reaction in a greater detail for, if proved to be general, it would habe a far reaching scope in modifying the existing procedures of:

(i) converting ROH ⟶ RH in sensitive molecules thus providing with shorter and milder methods for obtaining desoxy sugars and steroids which form part of the molecule of such physiologically important substances as nucleic acids (2-desoxy-D-ribose), cardiac glycosides (digitalose, cymarose) and steroids, bile acids and hormones;

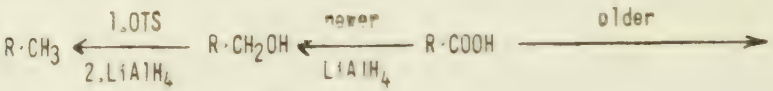
(i)

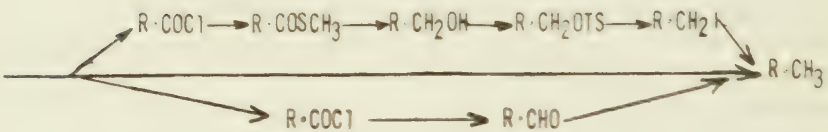


(ii)

(ii) converting >CO ⟶ CH_2, via -CHOH, wich is a milder alternative to Clemmenson's, Wolfrom-Karabinos's, and Kindlers catalytic methods, all invalid for acid sensitive substances, and to Wolff-Kishner's drastic reductions;

(iii) degradation of $R.COOH \longrightarrow R.CH_3$, via $-CH_2OH$, which is shorter than those already being used in di-and triterpenes[115] and also could be employed, as shown by karrer and coworkers[116], for converting optically active aminoacids to amines of the same number of carbon atoms without recemisation.



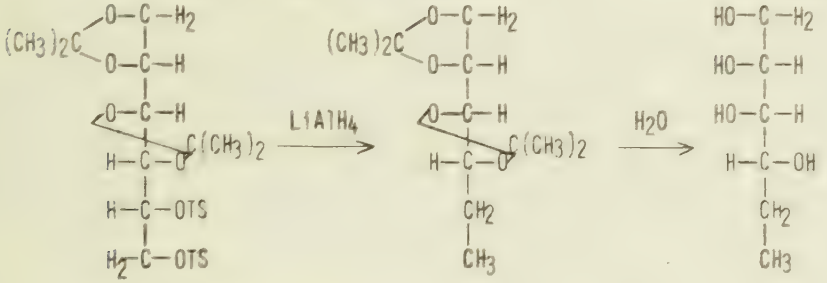


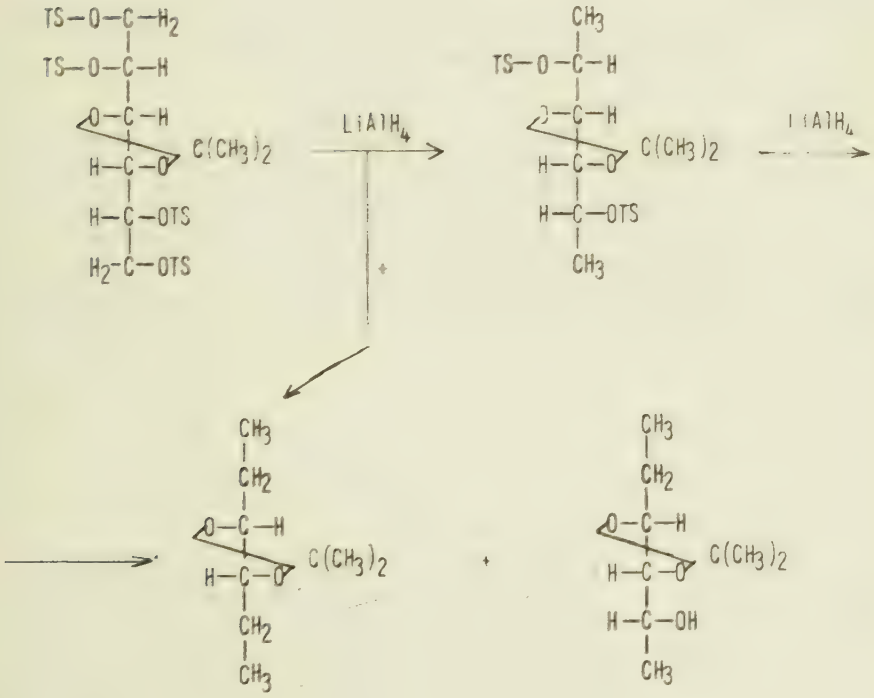
A. Desoxysugars Reduction of vicinial ditosylesters was to be studied.

(a) D-arabo-mannitol series

As was expected, both the primary and the secondary tosyl groups of 1:2:3:4-diacetone-mannitol-5:6-ditosylester got reduced giving 1:2:3:4-diacetone-5:6-bisdesoxy-D-arabo-mannitol in 40 % yield, which was better than that obtained by the NaI/acetone/H_2 method (25 %). Its further hydrolysis with N/10 H_2SO_4, at 60° gave the free desoxy compound, mp 122°, (92 % yield), which was identical with that of P. Karrer's D-arabo-3:4:5:6-tetrahydroxy-hexane[113c] obtained by NaI/H_2 method. Reduction of 3:4-acetone-mannitol-1:2:5:6-tetratosylester in benzene-ether gave 3:4-acetone-1:6-bisdesoxy-2.5-ditosylester, 21 %, with only a very small amount of the tetradesoxy compound showing that the primary tosyl groups were preferentially attacked. Use of tetrahydrofurane gave the desired tetradesoxy compound in 20 % yield with some 4-5 % of the above ditosylester, both calculated on the total weight. It was probably due to the lesser solubility of $LiAlH_4$ in the solvent mixture (cf. the reduction of cholesterol-3-tosylate in ether at room temp[100] as against the earlier refluxing[101] for 20 hours in benzene-ether). Reduction of the 2:5-ditosylester containing only isolated secondary tosyl groups yielded the tetradesoxy compound 23 %, with some 7 % of probably 2-desoxy-5-hydroxy-compound which showed that in such cases the $[AlH_4]^{\ominus}$ anion can simultaneously attack both the C—O

and the S—O bonds, while in the case of the primary tosyl groups the C—O bond is preferentially attacked.





EXPERIMENTAL:

The starting materials were prepared by the tosylation of mono-and diacetone-mannitol[117] in 95 % yield as against the earlier[113c] 80 %.

Reduction of diacetonemannitol-ditosyl ester:

4gm of powdered $LiAlH_4$ were added to 20gm of the ditosylester, dried at 45°/0.02mm, 3hrs, in 12cc benzene and 150cc ether. After the preliminary reaction was over, it was refluxed for 30 hrs, decomposed with ice-cold water, filtered over Hyflo-Supercel, and the solvent from the washed and dried ethereal layer was removed using a Widmer column. The residue, 10gm, which still gave a positive test for sulphur, was distilled in a kügelrohr under 0.02mm and the fraction coming upto 80° was collected. It was a colourless oily viscous liquid, 3.1gm, (40 %). The analysis was:

	C	H
Found,	62.58	9.76
$C_{12}H_{22}O_4$ requires,	62.61	9.56

which shows it to be 1:2:3:4-diacetone-5:6-bisdesoxymannitol. After 80° decomposition of the sulphur compounds sets in and makes further isolation of the diacetal difficult.

Hydrolysis: To 500mgm of the above acetal, in 5cc of alcohol, were added 15cc N/10 H_2SO_4, and the turbid solution thus obtained was warmed at 60° for 3 hrs. The clear solution was neutralized with $BaCO_3$, filtered after boiling with norit, and evaporated to dryness under reduced pressure. The residue, after crystallization, had a mp of 116 - 18° which after several recrystallizations from ethyl acetate rose to a constant value of 121.5-22°, and was indentical with D-arabo-3,4,5,6-tetrahydroxyhexane. Yield, 300 mg. The analysis was:

	C	H
Found,	47.92	9.33
$C_6H_{14}O_4$ requires,	48.00	9.33

Hydrolysis with N/50 H_2SO_4 at 40°/5hrs gave the same product.

Reduction of Monoacetonemannitol tetratosyl ester.

To 13gm of $LiAlH_4$ in one liter absolute ether were dropwise added 40gm of the tetratosyl ester, dried at 60°/0.02mm.5hrs, in 500cc of CaH_2-distilled tetrahydrofurane. After refluxing for 36hrs it was decomposed with cold water, filtered, and the ether from the washed and dried ethereal layer removed using Widmer coloumn, (bath temp 50-60°). The remaining solvent was removed by cooling the residue to -60°, applying 10mm vacuum, changing the cold bath from the container to the spiral reciever, thus distilling the tetrahydrofurane at room

temp. The process was repeated several times and mixed all the distillates (Distillate-A). Tetrahydrofurane was removed from this distillate at 50-60° without vacuum using a Widmer column and then from a small Claisen flask. The residue was mixed with the main residue, the whole of which was then repeatedly triturated with 30-40° pentane and kept at -10° overnight to precipitate the S-containing compounds. After repeating the process several times the residue was dried at 15°/10mm and repeatedly crystallized from 95 % alcohol to give colourless needles, mp 91.5-2.5°. 0.9 gm. The concentrated charcoaled mother liquor gave another 0.2gm (in all 1.1gm as against 5 gm obtained if the reduction is carried out in benzene-ether mixture). The analysis was:

	C	H	S
Found,	55.60	6.33	13.00
$C_{23}H_{30}O_8S_2$ requires,	55.42	6.02	12.85

which shows it to be 3:4 monoacetone-1:6 bisdesoxymannitol-2:5-ditosylate.

The pentane extracts. Pentane was removed over a Widmer column and then from a small Claisen flask at 30-60° and fractionated in a kügelrohr;

(a) Fraction I, 50-80°/10mm, colourless pleasant smelling oil;
(b) " II, 70-100°/0.02mm, pale yellow viscous oil, no smell,
(c) " III, 100-135°/0.02mm, Yellow very viscous oil, no smell;

The residue became too dark and decomposed. Fraction-I was refractionated to give: Distillate-B, 60-70°; Distillate-C, 70-90°; a dark residue. Distillate-C was still impure and so was further fractionated into: Distillate-E, 50-60°/60mm and Distillate-F, 70-80°/60mm. Distillate-E was pure tetradesoxy compound. Distillates-C & F were combined and refractionated when more of Distillate-E was obtained. The total yield was 1.5gm. The analysis was:

	C	H
Found,	68.28	11.19
$C_9H_{18}O_2$ requires,	68.35	11.40

Its bp was 50-60°/60mm, and for optical rotation, 157mgm in 10cc alcohol in a 1dm-tube, had a rotation of + 0.3°. So $[\alpha]_D^{20}$ + 19.05° (± 1.0)

Fraction-II had C, 62.52; H, 10.91, S, 2.09. 1gm of it was developed over alumina with 3:10 benzene-petrol-ether and the first five petrol-ether eluates, 10cc each, gave on working 150mgm of a S-free compound. Its redistillation gave an oil, C, 58.27; H, 10.52 which seemed to be a mixture of mono-and dihydroxylated compounds. The Small quantity didnot allow further work.
Further fractions from alumina and Fraction-III contained too much sulphur.

HYDROLYSIS: 300mgm were hydrolysed as for the other compound. It gave an oil which on distillation had C, 29.0; H, 11,68, while $C_6H_{14}O_2$ required C, 61.0; H, 11.86. This half C-content could not be accounted for.

Further reduction of the 2:5-ditosyl ester:

1gm $LiAlH_4$ was added to 4gm of the ester, dried at 45°/0.02mm, 3hrs in minimum benzene+ 80cc ether. After refluxing for 30hrs, it was worked up as usual. The residue was twice fractionated to give a colourless pleasant smelling oil. bp 50-60°/60mm, and analysis, C. 68.16; H, 11.60. So it was identical with the former tetradesoxy compound, yield, 30°mgm, 23 %.

The residue, after three refractionations in high vacuum, gave a distillate, bp 40-50°/0.02mm, and with the analysis:

	C	H
Found,	61.28	10.45
$C_9H_{18}O_3$ requires,	62.07	10.35

Found, Active-H, 0.34 Requires, 0.55.

Its yield was 100mgm, 7 %. So it seemed to be 2-desoxy-5-hydroxy compound ? its p-nitrobenzoyl ester could not be crystallized.

(b) meso-Inositol series

No tosylate of inositol was found to have so far been described though the hexaphosphate and some other esters are known. Difficulty in its tosylation arose due to its very slight solubility even in boiling pyridine (effect of 6-OH groups). It was found to be insoluble also in other polar solvents as collidine, dimethylaniline, dioxane, T.H.F., N-methylmorpholine, acetonitrile, benzonitrile, nitrobenzene, dimethylformamide. So it was decided to tosylate it at higher temp using prolonged heating to help the equilibrium shift to completion. The highest tosylate thus obtained was a tetratosylate, in 27 % yield, the rest being a mixture of di-and tritosylates. The following conditions were tried to find the optimum yield.

Amount of Inositol	Amount of TsCl in gms	Amount of TsCl in Mols per -OH	Temp. & Time	Amt. of (OTs)4	Yield %
1gm	8.5	1.3	20°/30hrs	Traces	----
3	25.5	1.3	60°/ 6hrs	2.1gm	15.7
5	65.0	2.0	60°/20hrs	6.0gm	27.0

Whether still more excess of TsCl (3-4 mols per -OH) and a longer time, say 100hrs, can increase the yield or give higher tosylates, if the steric factors allow it, remains to be seen. The position of the tosyl groups is not yet known. Rather it was thought to derive it from the study of the reduction product itself. The lower tosylates, which were soluble in pyridine, were retosylated using 1:2 mol TsCl, but the product was too soluble in alcohol showing failure to obtain tetratosylate. 8gm of the ester, on reduction in T.H.F., gave 545mg of an oil which resolved itself into 270mg of p-tolylmercaptan and 150mg of an oil, bp 60 70°/0.005mm, the analysis of which as such and as p-nitrobenzoyl derivative corresponded to hexantriol mixed with 25 % of hexandiol, i.e tri- and tetradesoxy compounds with opened cyclohexane rings but no definite proof was available. Though the fact that all known cyclohexandiols and triols are solids while open chain diols and most triols are known to be high boiling liquids seemed to support this view yet the opening of the ring is less probable. Tolylmercaptan probably arises from the reduction of the sulphinic acid formed from the hydrolytic fission of one of the tosyl groups. This ring opening, if confirmed, would be a unique example of $LiAlH_4$-reductions though nothing definite as yet can be said about these observations.

EXPERIMENTAL

meso-Inositol tetratosylate:

5gm inositol, dried over P_2O_5 at 100°/0.02mm, 5hrs, was boiled with 100cc of absolute pyridine, cooled to 60°, and added 65mg of freshly distilled TsCl, 1:2 mol ratio required 63.5gm, in 100cc pyridine. Maintained the temp for 20hrs when gradually the whole of inositol went into solution. After distilling most of the solvent under reduced pressure, poured it over ice, triturated the solid thus obtained with water, washed, dried, and triturated again with warm petrol-ether to dissolve the unreacted TsCl. The white residue was repeatedly extracted with boiling absolute alcohol (6 refluxings, 500cc each) to dissolve the lower tosylates, no crop of which after crystallization from alcohol or acetic ester, had a mp above 228-30°, with a S-content of 13-14 % which corresponded mainly to a mixture of di- and tritosylates. The alcohol-insoluble residue was twice crystallized from acetic ester, dried over P_2O_5 at 110°/0.02mm, 3hrs, and had a mp 275°. The analysis was:

	C	H	S
Found,	51.40	4.58	16.02
Tetratosylate, $C_{34}H_{36}O_{14}S_4$ required	51.25	4.52	16.08

Yield was 6gm, 27 %.

Reduction: To a cold solution of 8gm of the dried ester, dissolved by refluxing in 250cc of CaH_2-distilled Tetrahydrofurane, was added 5gm (a large excess, 1:3 mol) of $LiAlH_4$ in 100cc of Tetrahydrofurane. It was refluxed for 36 hrs, most of the solvent then distilled off, and the cold solution decomposed with ethylacetate and then with water. Filtered over HyfloSupercel, saturated the filtrate with CO_2 to precipitate LiOH, filtered and removed the solvent under reduced pressure. The alumina-cake was repeatedly extracted with hot alcohol, saturated with CO_2, filtered and the residue added to the main portion. The presence of sulphur and the Li-salts was still shown and so it was thoroughly dried and extracted with absolute benzene, the residue from which, after crystallization from ethylacetate, gave only some gummy crystals with oily droplets. It was distilled as follows:

Fraction-I, 125-30°/10mm, yellow oil; Fraction-II, 95-100°/0.005mm, colourless oil, 200mg. Fraction-I was redistilled into Fraction-III, 130-35°/0.005mm, yellow oil, 345mg. Their crystallizations still gave oily drops which were found to be insoluble in petrol-ether. So both the fractions were extracted with 30-60° petrol-ether, and the yellow oil 270mg, after removing the solvent, was chromatographed on alumina, III-IV grade, eluted with petrol-ether, and the colourless oil (260mg), on crystallization from petrol-ether and drying had a mp 44.5°, and an analysis:

	C	H
Found	68,39	5.93

It did not correspond to any known expected cyclohexandiol (mp 86-134°). It contained sulphur and resembled cresol in smell and was identified to be p-tolylmercaptan, mp 43°, and required,

C	H
67.8	6.45

Petrol-ether-insoluble oil (150mg) still contained sulphur its thorough drying gave an analysis

		C	H
	Found,	54.59	10.36
Cyclohexandiol, $C_6H_{12}O_2$	required,	62.07	10.34
Cyclohexantriol, $C_6H_{12}O_3$	"	54.54	9.09
Cyclohexantriol-monotosylate $C_{13}H_{18}O_5S$	"	54.54	6.29

To decide between cyclohexantriol and its tosylate, the oil was converted into its p-nitrobenzoyl derivative: 62mg in 1-2cc pyridine was treated with 337mg p-nitrobenzoyl chloride in 2-3cc pyridine, using 1:4mol, on the basis of the three-OH groups, left overnight and worked up as usual. Crystallization from alcohol gave pale yellow needles, mp 174°, which contained no sulphur now and had an analysis:

		C	H
	Found	55.33	4.22
Cyclohexantriol-tri-p-nitrobenzoate, $C_{27}H_{21}O_{12}N_3$	required	55.95	3.65

Its recrystallization and thorough drying gave the same mp, but the analysis was

		C	H	N
	Found	55.84	4.26	7.24
$C_{27}H_{21}O_{12}N_3$	required	55.95	3.65	7.25

This showed the original oil to be cyclohexantriol arising from the hydrolytic fission of one of the tosylgroups due, perhaps, to its spatial position in the molecule. But still the H-content was too high to be accounted for. The remaining 70-80mg of the oil was redistilled at 60-70°/0.005mm, when the S-free distillate had

	C	H
Found	55.69	10.98

This constant higher H-content and the high boiling oily nature of the product pointed to the opening of the cyclohexane ring to give hexantriol though it is less probable. The following tables compare the analysis-data of the compounds concerned.

Substance	Form	ANALYSIS		
		C	H	N
Free-ols:				
Cyclohexantriols	Solid	54.54	9.09	----
Cyclohexandiols	Solid	62.07	10.34	----
Hexantriols	Liquid	53.73	10.44	----
Hexandiols	Liquid	61.01	11.86	----
Nitrobenzoyl esters:				
Cyclohexantriol triester	Solid	55.95	3.65	7.25
Cyclohexandiol diester	Solid	57.97	4.34	6.76
Hexantriol triester	Solid	55.76	3.96	7.22
Hexandiol diester	Solid	57.69	4.80	6.73
ISOLATED REDUCTION PRODUCT:				
Free-ols	Liquid	55.69	10.98	----
Ester	Solid	55.84	4.26	7.24
COMPUTED VALUES on the basis of 25 % Diol + 75 % Triol:				
Cyclohexane series:				
Free-ols		56.42	9.40	----
Esters		56.45	3.82	7.13
Hexane series:				
Free-ols		55.55	10.80	----
Esters		56.24	4.17	7.10

These tables support the possibility that the reduction product maybe hexantriol mixed with 25 % of hexandiol, i.e. tridesoxy compound + 25 % of tetradesoxy compound with opened up rings. These observations have still to be further confirmed.

B. DESOXYSTEROIDS

(a) 4-hydroxycholesterol series

Reduction of cis-Δ^5-3:4-dihydroxycholestene-tosylate was to be studied. it gave only a monotosylate, in 89 % yield, which was taken to be the 3-tosylate due to the known reactivity of the C_3-OH in the steroids (cf. the order of reactivity in esterification[118] of steroids). The use of an excess of TsCl, even 1:3 mol per hydroxyl, could not force it beyond monotosylation. The tosyl group was not replaced by -OEt even when crystallized from alcohol (cf. cholesterol tosylate). Its reduction gave 75-80 % of a crude mixture which, on chromatography, gave two isomers mp 144° and 98°. (Chromatography of the reduction product of singly crystallized 3:4-diol tosylate gave three isomers, mp. 80°, 144°, 98°, while that of several times crystallized tosylate gave only the latter two isomers). Their properties, mode of formation, and structures are discussed below.

(i) Isomer mp 80°: was found to be Δ^4-cholestene (coprostene) arising perhaps from the reduction of a small quantity of ditosylate present in the singly crystallized monotosylate whose presence could not be revealed by analysis.

(ii) Isomer mp 144°: From analogy to the reduction of cholesterol tosylate, it was at first concluded to be Δ^5-4-hydroxycholestene. Its structure is proved below.

1. The Hydroxyl group: its presence was proved by its forming a p-nitro-benzoyl derivative, mp 173.5-75°, and its position was shown to be 4 (β) by its catalytic hydrogenation to Cholestan-4 (β)-ol, mp 189°.

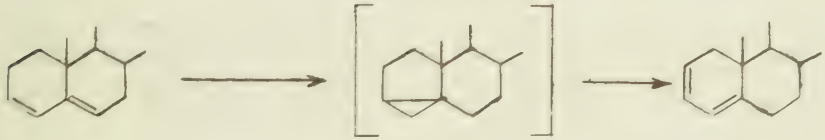
2. The Double Bond: Its presence was shown by a positive tetranitro methane-test, bromine-and perbenzoic acid absorption and finally by its infrared spectrum. Quantitatively, it absorbed one mol H_2, showing one double bond. It was thought to fix up its position by its conversion to the known Δ^5-cholestene by tosylation and subsequent $LiAlH_4$-reduction. The tosylation, however, gave only a pyridinium salt which was rather expected for an α-β-unsaturated alcohol. To avoid pyridine, it was converted into its 4-bromo-derivative to be treated with silver tosylate to form the 4-tosyl ester. The bromo-derivative would not

crystallize and so was directly converted into the trimethylamine ammonium salt to be distilled to give the known $\Delta^{3,5}$-cholestadiene thus proving the position of the double bond in the original molecule to be $\Delta^{5:6}$ Actually, however, this degradation gave an oil, which on chromatography, yielded a solid mp 54.5-58.5°, whose ultraviolet absorption showed it to be a mixture of $\Delta^{3,5}$, $\Delta^{2,4}$. dienes.

(The older literature mentions $\Delta^{2,4}$-diene having a mp 63 and max. 260mμ).[119]

Substance	MP	Max.
$\Delta^{2,4}$-diene	68.5°	275 mμ
$\Delta^{3,5}$-diene	80.0°	235 mμ
isolated	54.5-8.5°	235+260mμ

The possibility of the isomer mp 144° being Δ^{2}-cholesten-4β-ol, which can easily explain the formation of a mixture of the dienes ($\Delta^{2,4}$-diene, by the action of acids or by heat, is known to readily pass over to the stable isomer, $\Delta^{3,5}$ -diene[120]) is ruled out for such a dehydrotosylation of the 3:4-diol-3-tosylate would actually lead to $\Delta^{2,5}$-diene 4β ol and also that it occurs only under very drastic conditions as boiling in pyridine or pyrolysis, which is impossible in the specially mild $LiAlH_4$-reductions. On the other hand, the presence of the $\Delta^{2,4}$ -diene in the mixture may be accounted for by assuming it to arise from $\Delta^{3,5}$ -diene itself, the reverse migration of the double bonds, though not yet recorded in literature, taking place probably through an intermediate i-cholestene form. The inversion of optical rotation in these hydrocarbons also points in that direction.



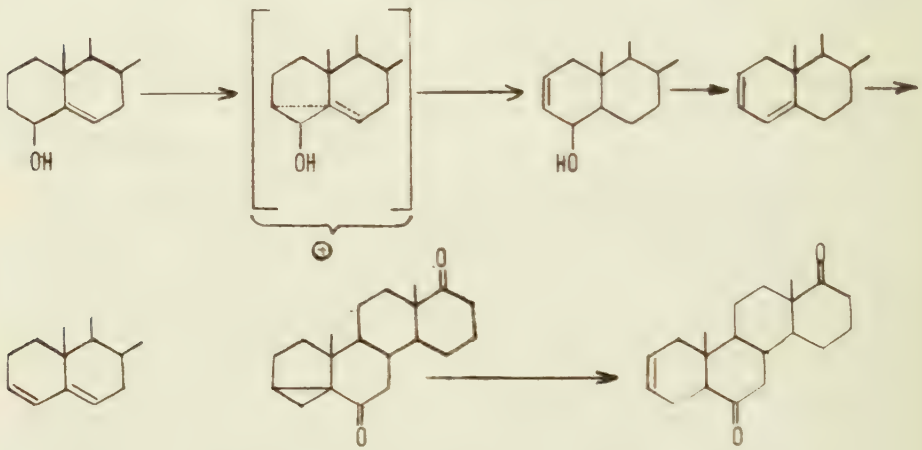
$[\alpha]_D$ -123° + 80° + 168,5°

(Actually some i-cholestene ion is involved as an intermediate and not i.cholestene itself whose $[\alpha]_D$ is given).

Besides, the parallel case of the conversion of i-androsten-6:17-dione into Δ^{2} -androsten-6:17-dione, by boiling in quinoline, and the fact that all earlier attempts to prepare $\Delta^{3,5}$ -diene invariably gave a mixture of $\Delta^{3,5}$ + $\Delta^{2,4}$-dienes support the view that this conversion can take place. (Incidently, it would also account for the lower values of the constants of $\Delta^{2,4}$ -diene in the older literature). Further, this conversion is far more probable in the case of 4-hydroxycholestene, for it involves a hydroxycyclopropane structure which, like vinyl alcohol, is unable to exist as such and so

readily opens up in the other direction giving Δ^{7} -cholesten-4β-ol which is the precursor of $\Delta^{2,4}$ -diene and thence of the mixture.

This evidence fixes up the position of the double bond to be $\Delta^{5:6}$, and proves the isomer mp 144° to be Δ^{5} -cholesten-4β-ol.

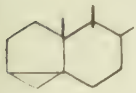


Further work: An Oppenauer oxidation of the isomer-144° to Butenandt's Δ^{5}-cholesten-4-one[121a], mentioned as "hetero- Δ^{1}-cholesten-3-one" in earlier literature[121b], and further its Wolff-Kishner reduction would give additional proofs of its structure. $LiAlH_4$ reduction of this ketone, at present prepared from cholestane, would constitute its real synthesis. It would also be interesting to find if the isomer-144° shares the estrogenic action of this ketone[121a]

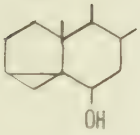
(iii) Isomer mp 98°: Was shown to be a cholestenol.

1. The double bond: It gave a positive tetranitromethane test, decolourised bromine and dil.alk.permanganate in the cold. Infrared spectrum showed a double bond. It absorbed one mol H_2 in presence of Pt giving a dihydro-compound mp 84° (a 4-hydroxy-3:4:5-cyclopropano-cholestane would have given cholestan-4β-ol, mp 189°), and one mol oxygen from perbenzoic acid to give an oxido-compound, mp 174°. Besides, its analogy to hydroxycyclopropane shows that no such natural or synthetic compound has so far been found to exist. In fact due to the unsaturation associated with the three membered ring, which is clearly marked in i-steroids too by their catalytic hydrogenation, lability to nucleophilic reagents, ultraviolet absorption of Δ^{6}-i-cholestadiene[122] and the formation of pyridinium salts by i-cholesterol instead of the normal tosylates, such a structure would correspond to vinyl alcohol and the ring would certainly open

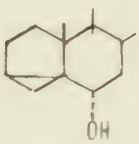
up in some way Further, it had a levoratation while all steroids are dextrorotatory.



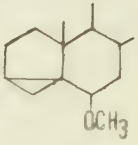
$[\alpha]_D$ + 79,6°



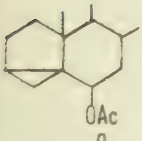
+ 24°



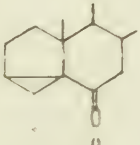
+ 60,9°



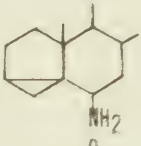
+ 55°



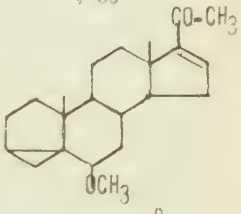
+ 48°



+ 41,0°



+ 20°



+ 87,4°

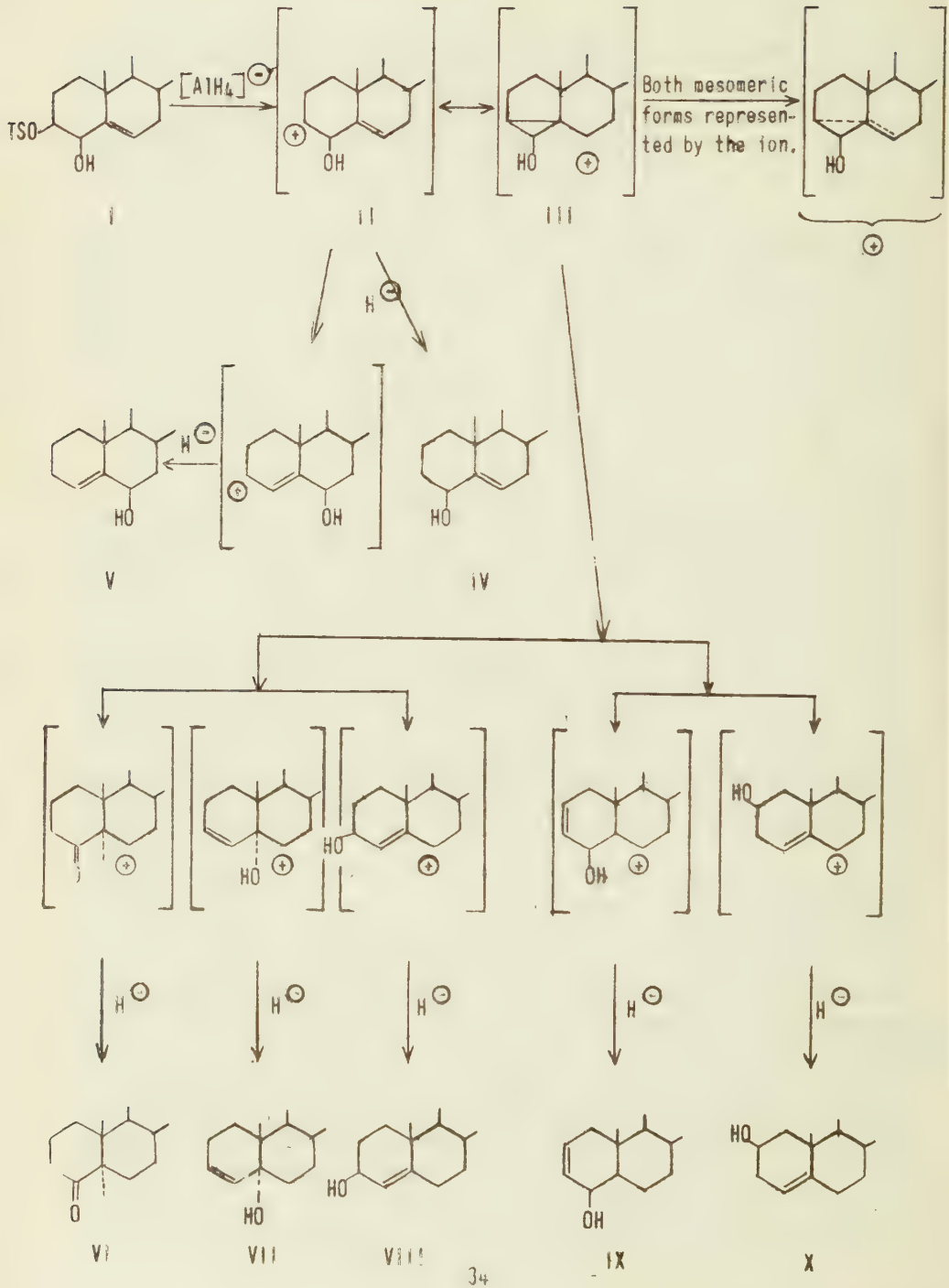
According to Callow-Young rule[123] all $\Delta^{5:6}$ -steroids have levorotations which changes to the dextro side on conversion to $\Delta^{4:5}$ - or saturated compounds. It is likely that the same change to dextrorotation is involved in the -steroids too which are generally formed by a migration of the π bond from the 5:6 to 3:5-position. That a -OH group directly attached to the ring may cause an exception to this rule is remote for such an attachment would make it so unstable as to be unable to exist at all. So all this evidence definitly proves the presence of a double bond though its position remains unknown.

2. The Hydroxyl group, Its presence was definitely shown by its forming a p-nitrobenzoyl derivative, mp 169-70°. Its dihydro-compound did not correspond to any known cholestanol or coprostanol and so its position remains unknown.

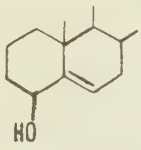
Its possible structure. The reduction of the diol-tosylate is represented on page 34.

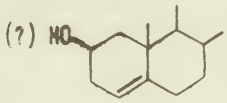
This reaction mechanism readily explains the formation of Δ^5-cholesten-4βol, IV, as the major product of reduction and also leads us to believe that the isomer-98° may have the structure X, Δ^4 -cholesten-2βol. The following argument may be considered:

Of all the possibilities considered above, structures VI, VII and VIII are straightway rejected for VI is ketonic, VII contains a tertiary -OH and would not form any ester, least the nitrobenzoyl, in such a hindered position, and VIII is the allo-cholesterol or its epimer. Only V, arising from II by the

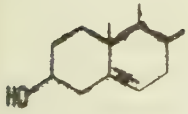

TSO
OH
[AlH4]
Both mesomeric forms represented by the ion.
HO
H
I
II
III
V
IV
VI
VII
VIII
IX
X

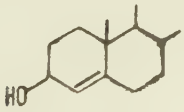
known isomerization of Δ^5-3·4-diols into Δ^4-3·6-diols[124], and IX and X, arising by the opening of the unstable hydroxycyclopropane ring (cf. opening of cyclopropanone ring in i-androstene derivatives[121a]), remain for consideration. V and IX, on hydrogenation, would have given cholestan-6βol and -4βol, mps 130° and 189° Now if we exclude their C_5-epimers by believing that Auwers-Skita rule here too holds good, the only structure possible for it seems to be X. The conversion of Δ^5 cholesten-4βol into cholestan-4βol and not coprostan-4βol which would normally be expected from this rule shows that in cholestenols the C_{10}-methyl which is situated at the bridgehead is more powerful in determining the mode of addition to the bridge head C_5-double bond and thus influences the configuration of the entering C_5-H. This justifies the exclusion of V and IX as possible structures for the isomer-98°. (The hydrogenation of cholestenes, however, seems to be inconsistent with this rule). The C_5-α configuration of V is also consistent with its being the precursor of $\Delta^{2,4}$-diene in the degradation of Δ^5-cholesten-4βol. Further the lower value of the optical rotation of isomer-98° also supports this structure (Callow-Young rule: $\Delta^{4:5}$-steroids have more dextrorotation than $\Delta^{5:6}$-compounds). As the epimerization produces too much dextrorotation in these compounds this argument would lead to Δ^4-cholesten-2βol as the most probable structure for the isomer-98°.

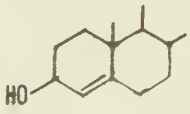




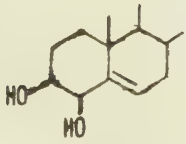
$[\alpha]_D$ - 55° - 87,2°



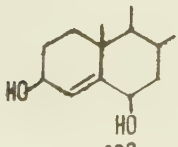




- 30° + 44° + 121°



- 60°



- 13°

EXPERIMENTAL:

To 4.8gm of 4-hydroxycholesterol[125], dried at 90°/0.02mm, 3hrs, in minimum of absolute pyridine were slowly added at 0° 4gm (1:1.3 mol ratio) of freshly distilled TsCl in minimum of pyridine. After keeping for 1/2hr at 0° and 70hrs at room temp, most of the pyridine was distilled off at 25° under vacuum, diluted with ice powder, and extracted with chloroform. The extract was washed, dried, the solvent removed and the residue crystallized from benzene and the mother liquor, after concentration, from benzene-petrol-ether. Mp 110-12°, yield was 5.7gm, 89.1 %. Its analysis was:

		C	H	S
	Found	73.50	9.38	5.60
$C_{34}H_{52}O_4S$	required	73.38	9.35	5.75

Use of excess of TsCl, 6gm for 1.8gm of the diol (1:3mol ratio) gave the same compound mp 103-5° and analysis still bad. Thus 4-OH remained untosylated.

Reduction:

To 5gm of the ester in minimum of benzene and 100 cc ether, 6 gm of $LiAlH_4$ was added, the contents refluxed for 16hrs, cooled, decomposed with cold water, filtered, and the aqueous layer extracted with ether. The combined ether solutions were washed, dried, the solvent removed and the residue crystallized from ethyl acetate. It gave snow-wite needles, mp 118-20°, melting slowly and not sharp. The analysis was:

		C	H
	Found	84.10	11.92
$C_{27}H_{46}O$	required	83.93	11.92

Yield was 2.6gm, 75 %. It was chromatographed as follows:
500mg of it was developed by 1:1 benzene-petrol-ether over 15gm Al_2O_3, II-III-

(A) Eluent, petrol ether-benzene, 4:1-mixture:

Fraction-I, 5cc, traces of yellow oil, only impurities;
" II, " colourless oil, crys. from alcohol, mp 78-80°
" III, " " " " " " 78-79°
" 4-9, " traces only;

(B) Eluent, petrol ether-benzene, 1:1-mixture:

Fraction 10-18, 8cc each, traces of brown oil;

(C) Eluent, Benzene:

Fraction 19-20,	8cc each,	traces of brown oil;		
" 21,	"	colourless oil, crys.	alcoho. mp	143°
" 22-25,	"	"	" "	144°
" 26-32,	"	"	" "	143°
" 33,	"	"	" Methanol,	128°
" 34-36,	"	"	" "	115-130°
" 37-38,	"	"	" "	100-120°
" 39-40,	"	"	" "	95- 98°
" 41,	"	"	" "	90- 92°
" 42,	"	traces.		

(D) Eluent, Ether, only traces.

Recrystallizations: (a) Fraction 2-3, from alcohol, mp 80-1°/10mg; (b) Fraction 21-32, from alcohol, mp 144°/250mg; (c) Fraction 33-38, from methanol, mp. 100-130°; (d) Fraction 39-40, from methanol, mp 98°/100mgm.

(a) Analysis of Isomer mp 80-1° was:

		C	H
	Found	87.32	12.36
$C_{27}H_{46}$	requires	87.59	12.41

Mixed mp with i-cholestene (mp 80-80.5°) was 70-76° and that with an authentic sample[126] of Δ^4-cholestene (mp 80-81°) was 81-2°, i.e. no depression. Thus it was identified to be Δ^4-cholestene (coprostene).

(b) and (c) Analysis of isomer mp 144°,	Found		83.85	11.89
98°,	"		83.89	12.10
$C_{27}H_{46}O$	requires		83.93	11.92

Isomer mp 144°: Optical rotation: 21.6mg in 2.2149gm (1.5cc) $CHCl_3$ in a 1-dm tube had a rotation of -0.80°, so $[\alpha]_D^{17.5} = -55.0°$

It gave a yellowish-brown colour with tetranitromethane, instantaneously decolourised bromine solution, and showed a double bond in the infrared spectrum. It absorbed perbenzoic acid.

p-Nitrobenzoyl ester: 10mg in 1cc pyridine were treated with 8mg of p-nitrobenzoyl chloride in 1cc pyridine, left overnight, diluted with water, washed with carbonate solution, then with water, dried and crystallized from alcohol, mp 173.5-75°.

Microhydrogenation: 30mg of the dried substance in 3cc pure glacial acetic acid were hydrogenated using 20mg of PtO. It absorbed 1.60cc at N.T.P. Theory requires 1.74cc. So it absorbed 0.92 mol H_2. The catalyst was filtered, the

solvent removed under vacuum, the oily residue triturated with water, cooled, washed until neutral, dried and crystallized from alcohol, mp 189°, corresponds with that of cholestan-4β-ol.

Degradation: Tosylation: 250mg of the dried substance were tosylated with 170mg TsCl in pyridine. Left at room temp for 30 hrs, distilled of most of the pyridine at 20° in high vacuum, poured over ice and extracted the resulting emulsion with chloroform. Evaporation of the solvent after washing and drying did not give any residue. The substance had formed a water-soluble pyridinium sal. Bromination[127]: To 400 mg. of the dried substance in 10-12cc absolute benzene were added in the cold 300mg (1:1 ratio) of twice distilled PBr_3 in 2cc benzene. Left overnight, poured over ice, and the solvent removed under vacuum from the washed and dried benzene layer. The oily residue, 220mg, did not crystallize. So it was taken up in 5-8cc dry benzene, in a microbomb tube, added excess of dry NMe_3, sealed the end and warmed to 80° for 6 hrs. Left overnight, washed the separated ppt with benzene and then ether and dried (210mg). The filtrate was evaporated under vacuum. The oily residue was insoluble in water, very sparingly solubie in alcohol, more so in benzene, acetic ester, and acetone, and gave no opt with $AgNo_3$. All this showed it to be a hydrocarbon probably arising from a partial degradation of the quarternary salt. it didnot crystallize, and so was distilled in high vacuum, but there too it decomposed.

Precipitate was soluble in water, (gave a foamy emulsion due to the large organic residue attached to it) and its solution gave a positive $AgNO_3$ test. it was soluble to some extent in organic solvents too but did not crystallize. It was directly treated with excess of Ag_2O (1.5gm) in methanol, shaken for 12hrs, filtered AgBr, concentrated, and distilled the residue in high vacuum: Fraction-I, 140-60°, a colourless oil. Fraction-II, 160-200°, a yellow oil, after that decomposition ensued. Both the fractions were developed with petrol ether over 10gm alumina, III grade, and eluted with petrolether. The colourless oil thus obtained was repeatedly crystallized from alcohol, mp 54.5-8.5°, its qualitative ultraviolet absorption showing a maximum at 235 mμ and another of half height, at 260 mμ, proving it to be a mixture of $\Delta^{3,5}$ & $\Delta^{2,4}$-dienes. Further separation was not successful.

Isomer mp 98°: Optical rotation: 119.4mg in 13.3835gm (9cc) $CHCl_3$ in a 1-dm tube had a rotation of -0.36°, so $[\alpha]_D^{18}$ -27.13°

it gave a yellow colour with tetranitromethane, decolourised bromine and dil.alk. permanganate solution in the cold and its infrared spectrum showed a double bond. it did not form any oxime, semicarbazone or dinitrophenyl-hydrazone. p-Nitrobenzoyl ester: 10mg of it was esterified in the same manner

as the other isomer and crystallized from alcohol, mp 169-70°. Mixed mp with the same ester of the other isomer, 145-55°. The analysis was,

	N		N
Found	2.77	$C_{34}H_{49}O_4N$ requires	2.62

Microhydrogenation. 30mg of the dried substance were hydrogenated in 3cc. pure glacial acetic acid, using 10mg of PtO. It absorbed 1.73cc at N.T.P. Theory requires 1.74cc. So it absorbed 0.993 mol H_2. It was worked up in the same way as the other isomer, crystallized from alcohol, mp 84°.

Oxide formation. 100 mg of the dried substance were dissolved in 3cc of 0.112M/ perbenzoic acid. A blank with 3cc per-acid was run simultaneously. After 15hrs, 0.2cc of the blank required 0.45cc N/10 $Na_2S_2O_3$, i.e. it was 0.112 M. 0.2cc of the substance required only 0.05cc of $Na_2S_2O_3$. So it absorbed 3cc M/10 instead of 2.6cc M/10 peracid, i.e. 1.15 mol oxygen.

After diluting with water, it was washed, dried, evaporated, and the residue crystallized from methanol, mp 86.5-87.5°. The analysis was:

		C	H
	Found,	79.75	11.39
$C_{27}H_{46}O_2$	requires,	80.59	11.44

(b) Δ^5-Pregnene Series:

Na/amyl alcohol reduction of cholesteryl chloride[128] yields only Δ^5 cholestene while that of cholesteryl tosylate with $LiAlH_4$ gives two isomers, Δ^5 cholestene + i cholestene, the latter arising from the reduction of the mesomeric cholesteryl-cation. The reduction of pregnenolon-3-tosylate was undertaken to confirm if it was a general phenomenon in this series. Its tosylation was affected in 97.5 % yield as against the earlier[129] 46.6 %, but its reduction introduced a new assymmetric carbon atom (C_{20}-OH) yielding a mixture of several isomers, the chromatographic separation of which as such and as acetates (to protect the sensitive C_{20}-OH) was unsuccessful. Chromic acid oxidation of the crude product gave a mixture of two isomeric C_{20} ketones, chromatography of which yielded the expected Δ^5 pregnen-20 one, but the i-isomer could not be isolated.

EXPERIMENTAL:

1. Toxylation: To 1gm of pregnenolone, dried at 90°/0.02 mm, 5hrs, in minimum of pyridine, was slowly added at 0° 0.9gm of freshly distilled TsCl in 3cc pyridine. Left at room temp for 48hrs, distilled off most of the pyridine at 20° in high vacuum, using a spiral receiver cooled to -60°, diluted with ice powder, and extracted with benzene. After the usual washing, drying, removing the solvent under vacuum, the residue was crystallized from benzene and the concentrated mother liquor from benzene-petrol ether mp 140-41°, yield 1.45gm, 97.5 %. Butenandt mentions 46.6 % yield using 1:2.3 mol ratio (ours was 1:1:3).

Reduction: To 1.45gm of the dried ester in 5cc benzene and 100cc ether was added 0.6gm $LiAlH_4$. Refluxed for 16hrs, decomposed the cooled contents with cold water, filtered and removed the solvent from the washed and dried ethereal layer. Crystallization from petrolether gave a snow-white product, mp 121-25°. Its analysis was:

		C	H
	Found,	83.18	11.35
$C_{21}H_{34}O$	requires,	83,44	11.25

600mgm of this product, in minimum of glacial acetic acid, was treated at 0° with a cold solution of 270mg (2 O) of chromic acid, dried at 50°/0.02mm, 2hrs, in 15cc glacial acetic acid. It was kept at 0° for 15 minutes and then left overnight. Diluted with water and extracted with ether. Washed the ether extract with bicarbonate and then with water, dried over Na_2SO_4, and the solvent removed. The crude residue, 120mg, 20 %, was developed with 1:5 benzene-petrol ether over neutral II-III grade alumina.

1. Petrol ether, 12 fractions, 4cc each, contained practically nothing;

2. 10:1 petrol ether-benzene, 20 fractions of 4cc each, then 6 fractions of 10-30cc, all solid crystalline products;

3. Further increasing the benzene-content of the eluent gave no solid.

Crystallisation: The first ten fractions of No. 2 above were crystallized from petrol ether, 30-40°, at -20°. Mp 111-12°, and the analysis was:

			C	H
		Found,	83.95	10.94
Pregnen-20-one,	$C_{21}H_{32}O$,	requires,	84.00	10.66

Its infrared spectrum showed the presence of a double bond. So it was the Δ^5-compound. The mother liquors and the rest of the fractions, after many similar crystallizations, gabe a product, mp 102-3°, which was impure. No i-isomer could be isolated.

REFERENCES

(The literature up to April 1951 has been reviewed)

1. Finholt, Bond and Schlesinger, Am Soc., 69, 1199, (1947).
2. Nystrom and Brown, ibid., 69, 1197, (1947).
3. Chimia, 5, 25, (1951), ref. 11, 12, 13, 14, 15.
4. T.R.P. Gibb jun., Metal Hydrides, Inc., U.S. Pat. 2468260.
5. Chimia, 5, 28, (1951).
6. Am Soc., 70, 3712, (1948), 71, 305, 761, 1624, 3925, (1949).
7. Badger et al., Soc., 2326, (1950); Am Soc., 71, 3664, (1949), 72, 1240, (1950).
8. (a) General: Levin, Am Soc., 70, 2958, (1948); Soc. 384, (1951); (b) 3-keto: Birch, Soc., 687, 2325, (1950); McKennis, J.Biol. Chem., 175, 217, (1948); Helv., 32, 265, (1949); (c)-6-keto: Wagner, Am Soc., 72, 1047, (1950); (d) 7-keto: Fieser, Am Soc., 71, 2226, (1949); (e) 11-keto:Sarett, "Fieser: "Nat. Prdts. Phenan". 1949, p 410;(f) 17-keto: ibid., p 326-7, 410; Am Soc., 71, 3689, (1949), 72, 882, 1323, (1950); Nature, 166, 107, (1950); Hel., 32, 1978, (1949); Canad. J. Res., 27B, 902, (1949); (g) 20-keto: Hel., 31, 2210, (1948); Soc., 1972 (1950); Am Soc., 71, 756, (1949).
9. F. Sörm, Collec. Czech. Chem. Comm., 14, 98, 273, (1949); Rec., 69, 368, (1950); Bull. Soc. Chim., 5, 17, 720, (1950).
10. Whitkop, Am Soc., 70, 3712, (1948), 72, 614, (1950), 71, 761, (1949); Helv, 33, 150, (1950); J. Org. Chem., 14, 862, (1949), 15, 790, (1950).
11. Everette et al., Am Soc., 73, 1301, (1951), ibid., 69, 1197, (1947), 70, 4265, (1948), 71, 57, 2058, 4141, (1949); J. Org. Chem. 13, 663, (1948), 15, 873, (1950).

12. Fieser; "Nat. Prds. Phenan.", 1949, p 327; Soc., 687, (1950); Am Soc 72, 1047, (1950); Hel., 32, 1692, (1949).

13 Am Soc., 73, 846, (1951).

14. Conover and Tarbell, ibid., 72, 3586, (1950).

15. Arens & Dorp, Rec., 68, 604, (1949); Inhoffen, Ann., 565 35 (1949); Am Soc., 71, 3267, (1949), 72, 234, 727, 3726, (1950).

16. ibid., 71, 3252, 3595, (1949).

17. (a) Booth, Soc , 1188 (1950); (b) Am Soc., 70 3738, (1948), 71, 305, 1675, (1949).

18. P. Karrer & C.H. Eugster, Helv., 32, 1934, (1949) Johnson, Am Soc., 72, 3726, (1949).

19 Trevoy & Brown, ibid., 71, 1675, (1949).

20. Lutz, ibid., 72, 2002, 4091, (1950); (a) idem., ibid., 72, 5511, (1950)

21. Helv., 33, 1093, (1950); Am Soc, 71, 122, (1949); Canad. J. Res., 27 B, 902, (1949).

22. Marvil, Am Soc., 73, 481, (1951); ibid., 71, 756, (1949), 72, 367, (1950).

23. Am Soc., 71, 3689, (1949); Helv., 32, 1758, 1978, (1949).

24. Am Soc., 71, 3689, (1949).

25. Dornow, Chem. Ber., 83, 445, (1950); Am Soc., 69, 2548, (1947), 71, 1624, 1675, 2856 (1949), 72, 727, 2195, 2827, 3878, (1950), 73, 722, 1038, (1951); J. Biol. Chem., 183 223, (1950). Soc., 873, (1950); Rec., 67, 489, (1948); Helv., 33, 1251, 1308, (1950).

26. Am Soc., 69, 2548, (1947).

27. Stoll, Helv., 33, 1308, (1950). Comp. Red., 230 485, (1950) Canad. J Res., 27B, 902, (1949).

28. Ruzicka, Helv., 33, 896, (1950).

29. Chem. Ber., 83, 445, (1950) Am Soc., 70, 3770 (1948), 71, 57, (1949), & ref. 26.

30. Wüest, Helv. 32, 443, (1949); Rec., 68, 604, (1949); Am Soc., 69, 2247, (1947); Distillation Produts, Inc., Brit. Pat., 633711.

31. Am Soc., 69, 2548, (1947), 70, 1981, 3857, (1948), 71, 57, 305, 2734, (1949).

32. ibid., 70, 1968, 1981, (1948), 71, 1710, (1949), 72, 1806, 3370, (1950), & ref. 2.

33. Anderson, Soc., 1037, (1950); Am Soc., 71, 305, (1949) & Ref. 2

34. Weygand, Chem. Ber., 83, 394, (1950); Canad. J. Res., 27B, 902, (1949).

35. P. Brandt, Acta Chim. Scandan., 3, 1050, (1949).

36. Am Soc., 70, 3314, (1948), 71, 305, 2683, 2899, 3460, 3618, (1949), 72, 1359, (1950); Chim. Ind., 677, (1950); G., 79, 856, (1950); Soc., 1037, (1950); Helv., 34, 117, (1950).

37. Am Soc., 73, 818, (1951).

38. ibid., 71, 879, 2444, 3541, 3994, (1949), 72, 2134, (1950); 73, 107, (1951); Soc. 663, 1720 (1949); Helv., 32, 1034, 1936, 1947, (1949), 33, 150, 164, (1950).

39. Am Soc., 71, 4160, (1949); Soc. 2393, (1950); Helv., 31, 1844, (1948), 32, 647, 1758, (1949), 33, 1088, (1950).

40. ibid., 32, 46, 2556, (1949), 33, 1129, (1950); Am Soc., 70, 1981, (1948); 72, 3314, 3800, (1950); Comp. Rend., 230, 485, (1950).

41. Am Soc., 71, 879, (1949).

42. Helv., 31, 1617, 2088, (1948), 32, 1034, 1156, 1936, (1949), 33, 302, (1950).

43. ibid., 32, 2003, (1949); Am Soc. 72, 147, (1950).

44. Helv., 32, 1947, (1949).

45. Inhoffen, Ann., 565, 35, (1949); Am Soc., 69, 2247, (1947), 71, 3267, (1949); Helv., 32, 436, 443, (1949); Rec., 69, 851, (1950); Chimia, 4, 104, (1950).

46. Am Soc., 71, 4160, (1949); Helv., 31, 1844, (1948).

47. Smith, J. Org. Chem., 15, 74, (1950); Am Soc., 70, 2601, (1948).

48. Am Soc., 72, 2305, (1950).

49. ibid., 71, 1624, (1949).

50. Soc., 1983, (1950).

51. Am Soc., 70, 1023, (1948).

52. Bachmann, ibid., 71, 3222, (1949).

53. ibid., 73, 847, (1951), & ref. 3.

54. P. Karrer & P. Banerjea, Helv., 32, 1692, (1949), ibid., 33, 1308, (1950); Am Soc., 70, 3738, (1948), 71, 305, (1949), 72, 158, 2998, (1950); Soc., 71, (1950); J. Org. Chem., 15, 1093, (1950); Bull. Soc. Chim., 5, 17, 720, (1950); Comp. Rend, 230, 485, (1950); Chem. Ber., 83, (1950).

55. Am Soc., 73, 201, (1951).

56. Schlitter, Helv., 31, 1397, (1948), ibid., 31, 2088, (1948), 32, 69, (1949), 33, 1093, (1950); Am Soc. 70, 3738, (1948), 71, 305, 2899, (1949), 72, 1359, 2880, (1950).

57. Zaugg, Anal. Chem., 20, 1026, (1948); Am Soc., 72, 2657, (1950).

58. J. Org. Chem., 14, 862. (1949) & ref. 56.

59. Experientia, 6, 377, (1950).

60. Chem. Ber., 83, 445, (1950); Am Soc., 70, 2286, (1948), 71, 2210, (1949) & ref. 57.

61. Swan, Soc., 1720, (1949); Am Soc., 71, 1694, 3206-7, (1949), 72, 1141, (1950); J. Org. Chem., 15, 003, (1950) & ref. 57, 59.

62. Am Soc., 71, 1694, (1949) & ref. 62.

63. P. Karrer et al., Helv., 33, 294, (1950).

64. ibid., 33, 1955, (1950).

65 ibid., 33, 2254, (1950).

66. Helv., 32, 544, (1949); Soc., 2095, (1949).

67. Wilk, J. Org. Chem. 15, 1020, (1950).

68. Ann. Rept. Chem. Soc., 46, 144, (1949), ref. 52, no experimental details, however, are given.

69. Witkop, Experientia, 6, 183, (1950); Am Soc., 72, 614, 1245, 3586, (1950).

70. P. Karrer & O.K. Patel, Helv., 33, 802, (1950) ref 2; ibid., 32, 22, (1949); Am Soc., 70, 3955, (1948), 71, 3460, (1949), 72, 3878, (1950).

71. H. Schmid & P. Karrer, Helv., 33, 863, (1950), (a) ibid., 33, 1093, (1950); Am Soc., 72, 2311, (1950); Soc. 1485, (1950).

72. P. Karrer & A. Chatterjee, Helv., 33, 802, (1950).

73. Am Soc., 72, 1645, (1950).

74. Elderfield, Am Soc., 72, 1334, (1950) & ref. 72.

75. Am Soc., 73, 504, (1951).

76. P. Karrer & O. Rüttner, Helv., 33, 812, (1950).

77. Am Soc., 70, 3738, (1948) & ref. 19.

78. Helv., 31, 1885, 2210, (1948), 32, 265, 275, 587, 1070, 1306, (1949); Am Soc., 71, 756, 3362, (1949), 72, 367, (1950).

79. Prelog, Helv., 33, 158, (1950).

80. Am Soc., 70, 3955, (1948); Reichstein, Helv., 32, 22, (1949).

81. H. Schmid & K. Kägi, Helv., 33, 1582, (1950).

82. King, Am Soc., 71, 3556, (1949).

83. Helv., 33, 1308, (1950).

84. Kenner & Murrey, Soc. 406, (1950).

85. Trans. Farad. Soc., 37, 607, (1941).

86. Am Soc., 66, 849, (1944), 67, 860, (1945).

87. P. Karrer et al, Helv., 32, 960, (1949), 33, 294, 555, (1950); Mathews, J. Biol. Chem., 176, 229, (1948).

88. Collec. Zchec. Chem. Comm., 12, 71, (1947).

89. Soc., 108, (1950).

90. Comp. Rend., 230, 304, (1950); Larson, Svensk. Kem. Tidskr., 61, 242, (1949) & ref. 36.

91. Am Soc., 71, 2946, (1949).

92. J. Org. Chem., 15, 81, (1950) & ref. 17b, 19, 25a. (a) Mislow, Am Soc., 73, 242, (1951).

93. Henne, ibid., 72, 3370, (1950) & ref. 59.

94. Helv., 33, 1093, (1950).

95. Am Soc., 71, 2210, (1949), 72, 2781, (1950); Helv., 33, 912, (1950), 34, 144, (1951); J. Org. Chem., 15, 807, 1003, (1950).

96. Am Soc., 72, 4327, (1950).

97. Am Soc., 70, 1023, 1968, 3664, 3738, (1948), 71, 1675, 1710, 3262, 4160, (1949), 72, 1806, 3370, 3796, 4547, 5511, (1950).

98. ibid., 71, 1786, 3970. (1949).

99. P. Karrer & M. Seyhan, Helv., 33, 2209, (1950).

100 J Starling et al, Rec., 69, 638, 909, (1950); Am Soc., 72, 731, 1033, (1950); Chem. Eng. News., 28, 3328, (1950); Am Soc., 70, 1023, (1948), 71, 3689, (1949). 72, 3716, 3796, (1950); Helv., 33, 302, (1950).

101. H Schmid & P. Karrer, Helv., 32, 1371, (1949). P. Karrer & G. Widmark, ibid., 34, 34, (1951).

102. Kenner & Murrey, Soc., S178, (1949).

103.. Am Soc., 70, 3484, (1948), 71, 2210, (1949), 72, 2781, (1950); J. Org. Chem.,15, 807, 1003, (1950); Helv., 33, 912, (1950) & ref. 2, 17b, 26, 54a, 60a.

104. Am Soc., 71, 4140, (1949).

105. Isaac Goodman, Soc., 846, (1951).

106. Sampey & Cox, Am Soc., 71, 1507, (1949).

107. Chimia, 5, 26-7, (1951).

108. Wendler, Am Soc., 71, 1140, (1949).

109. Am Soc., 70, 441, (1948); Warne, Nature, 165, 563, (1950).

110. P. Karrer & R. Schwyzer, Rec., 69, 474, (1950).

111. Runge: "Organomagnesiumverbindungen", 1932, (a) ibid. P48, 176, 178.

112. Dewar. "Electronic Theory of Org. Chem.", 1949, p62, 25-7, 115.

113. Nature, 163, Jan. 22, (1949); Helv., 29, 360, 378, (1946); (c) Helv., 31, 1611, (1948).

114. Am Soc., 72, 561, (1950).

115. Helv., 29, 360, (1946), 31, 2143, (1948).

116. Private Comm.

117. Soc., 13, (1946).

118. Fieser: "Phenan." p. 126.

119. Elsev. Ency. 14, p.18.

120. Fieser: "Phenan." p. 75, 252-3.

121. Butenandt, Ber. 75, 591, (1942); (a) Ber., 77, 397, (1944); (b), Ber., 68, 2091, (1935).

122. Am Soc., 66, 88, (1944).

123. Proc. Roy. Soc., A157, 194, (1936).

124. Soc., 135, (1943).

125. Soc., 377, (1937).

126. Soc., 347, (1928).

127. P. Karrer & Stähelin, Helv., 28, 438, (1945).

128. Monatsh, 15, 85, (1894).

129. Butnandt, Ber., 70B. 1446-50, (1937).

130. H. Schmid & K. Kägi, Helv., 33, 1582, (1950).

131. Soc., 59, 137, (1937).

132. Soc., 1459, (1937).

133. P. Karrer & Br. Jirgenson, Helv., 13, 1099, (1930).

CURRICULUM VITAE

I, Kunti Nandan Sareen, was born on June 3, 1919, (Jeth 18, 1976), in Srinagar (Kashmir), India. After getting the ten-years early schooling I matriculated in 1935 to join Forman Christian College, Lahore, to attend a five-years Natural Science course of the University of the Punjab leading to the degree of Bachelor of Science (Honours) in Chemistry, which I received in 1940. I started a research problem under the direction of Professor Dr. J.N. Ray, of the same university, whence, in 1941, I obtained the degree of Master of Science (Honours-School), with Organic Chemistry as my special subject. The cirumstances didn't allow me to continue my studies further and so I worked for some two years in the same university as a demonstrator to the Honours classes and as a Foods & Drugs Analyst, then for some three years as a lecturer in chemistry in a local college at Lahore, and finally for some two years as Chemist, Department of Pharmacology & Therapeutics, Medical College, Amritsar, from where I got leave to complete my studies at the University of Zürich- an old ambition which I could achieve only after waiting for eight years. I commenced the foregoing work for the Doctor's degree under the guidance of Professor Dr. Paul Karrer in April 1949 and completed it in March 1951.